 RESEARCH ARTICLE

Intracellular Molecular Pathways and the Biosystems that Arise from Them: An Ontological Investigation

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The cell's ability to metabolize foodstuffs, synthesize proteins and nucleic acids, and transduce extracellular signals, all rely on an intricate intracellular network of biological systems. These biosystems are the dynamic manifestations of the molecular pathways that define them and arise when these molecular pathways are activated. In this paper, I ask if the transformation from pathway to biosystem (abbr., bioS_{ip}, for intracellular pathway biosystem) is accompanied by a change in ontological status, and if so, what this new status is. After introducing key biochemical concepts, including the difference between pathway and biosystem, and the concept of enzyme coupling that transforms an ensemble of enzymes into a bioS_{ip}, I analyze the ontological status of bioS_{ip}s, specifically asking if the empirical data support the view that bioS_{ip}s exist in nature as ontological unities, as actualities. I conclude that certain highly structured bioS_{ip}s, known as metabolons, are indeed actualities. Finally, I explore the metaphysical foundations for the ontological unity of metabolons, considering three metaphysical systems that emphasize the dynamic and relational nature of reality: process philosophy, Aristotelian-Scholastic substance philosophy, and Ivor Leclerc's philosophy of nature.

Keywords

metabolic pathways • ontology • process philosophy • Aristotelian-Scholastic philosophy • Ivor Leclerc

1 Introduction

Recent years have witnessed something of a 'process turn' in the philosophy of biology (Dupré and Nicholson 2018; Jaeger and Monk 2015; Nicholson and Dupré 2018). Recognizing the dynamic and relational nature of the physical entities that populate the biological world, philosophers and scientists alike have argued that these entities are more accurately viewed as processes than as substances. These entities include enzymes, proteins, and other macromolecules (Alassia 2022; Guttinger 2018; 2021; Stein 2005; 2006; 2022), cells and single-celled organisms

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(Delafield-Butt 2007; Nicholson 2018; 2019), and multi-cellular organisms, including humans (Dupré 2015; 2020; 2021; Meincke 2018; 2019; 2021).

Counter these processual interpretations of biological entities are arguments asserting that an Aristotelian or Neo-Aristotelian substance ontology is more than adequate in providing metaphysical underpinnings for the dynamic and relational nature of these entities (Austin 2016; 2017; 2020; Austin and Marmodoro 2017; Steward 2020; Morgan 2021).

While differing in detail, both process ontology and Aristotelian substance ontology are anti-reductionist and regard biological entities as ontological unities. Opposed to these ontologies is the prevailing scientific view of reductionism, where every thing can be reduced to a set of basic elements (e.g., atoms, subatomic particles). Thus, organisms and other biological entities are, in effect, not real, and lack ontological status.

I enter this debate by drawing our attention to the interior of the cell and considering a level of biological complexity that lies between macromolecules and the whole cell itself. Our concern here will be with that subset of biosystems[1] that arise from operation of intracellular pathways.[2] Intracellular pathways map the sequence of enzymatic reactions that convert one chemical substance into another and include metabolic pathways (e.g., the glycolytic pathway) and signal transduction pathways (e.g., the insulin signaling pathway). The biosystems that emerge from the engagement and operation of pathways, $bioS_{ip}$s, play critical roles in the physiology of mammalian cells and microorganisms. In this paper, I will be concerned with the ontological status of $bioS_{ip}$s.

My investigation of $bioS_{ip}$s proceeds as follows. In the next section, I depict and analyze a simple, hypothetical metabolic pathway. This analysis allows basic pathway concepts to be illustrated and highlights the dynamic and relational nature of biosystems. In section 3, I explore the ontological status of $bioS_{ip}$s, where my chief concern is to establish whether $bioS_{ip}$s are mere assemblies of enzymes or functional wholes.[3] While this is primarily an empirical question that is answered by scientific investigation, certain metaphysical principles[4] are introduced to aid this discussion. Here I conclude that $bioS_{ip}$s do, in fact, exist as functional wholes. Furthermore, certain of these $bioS_{ip}$s that possess a structural integrity rise to the ontological status of actuality. In section 4, I introduce three metaphysical systems: process philosophy, Aristotelian-Scholastic substance philosophy, and Ivor Leclerc's philosophy of nature. Each gives a distinct account of how to explain the unity of the complex physical entities of the world. These systems will help us identify the metaphysical underpinnings that support the existence of those $bioS_{ip}$s that have the ontological status of actualities.

1. *Nomenclature and abbreviations:* In this paper, I take the terms 'biological system' and 'biosystem' to have the same meaning and will use them interchangeably. Biosystems include intracellular pathways, cells, organisms, and systems of organisms, such as ecosystems, and are abbreviated $bioS_{ip}$, $bioS_{cell}$, $bioS_{org}$, and $bioS_{eco}$, and their plural as $bioS_{ip}$s, $bioS_{cell}$s, $bioS_{org}$s, and $bioS_{eco}$s.

2. I distinguish between pathways and systems. While a pathway is a construct that maps the connectivity among the components of a system, a system is the dynamic manifestation of that pathway. More will be said about these concepts in section 2.

3. In section 3, I will clearly distinguish between two terms I use: functional whole and actuality.

4. Here, I take Clarke's (2001, 80) use of 'principle', as "that from which something flows, either in thought or in being." Thus, principle is a root, or ground, or source.

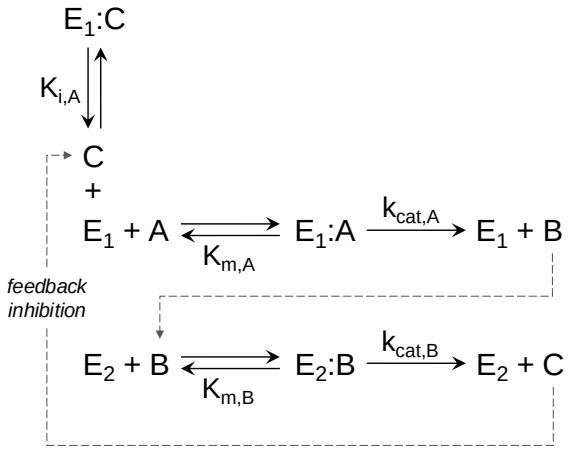

Figure 1: Schematic depiction of a metabolic pathway with feedback inhibition. $K_{m,A}$ and $K_{m,B}$ are dissociation equilibrium constants for the two complexes, E_1:A and E_2:B, respectively, and $k_{cat,A}$ and $k_{cat,B}$ are the catalytic rate constants for reaction of the two complexes to form product. $K_{i,A}$ is the inhibition constant for feedback inhibition of E_1 by C.

2 Intracellular Pathways and bioS_{ip}s: Key Biochemical Concepts

2.1 Differentiating Systems from Pathways

Before we begin our discussion of the biochemical concepts that are key to understanding bioS_{ip}s, I need to explain how I use the terms "pathway" and "biosystem." In this paper, I use pathway to refer to the sequence of enzyme-catalyzed reactions that converts one biochemical substance into another. As such, pathways are not actual things that exist in nature, but rather are constructs, often depicted schematically as maps that lead from the initial, starting substrate to the final product, through a series of enzyme-catalyzed reactions (for examples, see figures 1 and 5 below). What exist in nature are the enzymes and metabolites[5] that are referenced in these schematic depictions, as well as the biosystems that emerge from pathways that are triggered into operation. Thus, while an intracellular pathway maps the connectivity among the component enzymes and metabolites of the pathway, a biosystem is the dynamic manifestation of that pathway.

2.2 A Primer on Metabolic Pathways and the Biosystems that Arise from Them

To help our discussion, I've depicted a simple metabolic pathway in figure 1. This pathway is less complex than those often encountered in nature but will still allow basic concepts to be illustrated. In the first step of this pathway, substrate A reversibly combines with enzyme E_1 to form the molecular complex E_1:A. Within this complex, A undergoes a chemical reaction

5. This discussion of metabolic pathways needs to be prefaced by several comments about the central elements that comprise these pathways – enzymes and metabolites. Enzymes are protein catalysts that accelerate the critical reactions of an organism's metabolic and catabolic processes. All enzymatic reactions proceed by mechanisms in which the reactant molecule (or 'substrate', as it is known in the scientific literature) is bound by an enzyme within a micro-environment that is known as the 'active site'. Within the enzyme's active site, chemical transformation of substrate to product occurs. After completion of the reaction, the product dissociates from the active site and liberates the enzyme for another round of catalysis. Introduction to key concepts of enzymology, including the definition of the parameters of the legend of figure 1, can be found in the first several chapters of Stein (2011). 'Metabolites', as I use the term in this paper, refers to all the substrates and products of the enzymatic reactions that are defined in the description of a pathway.

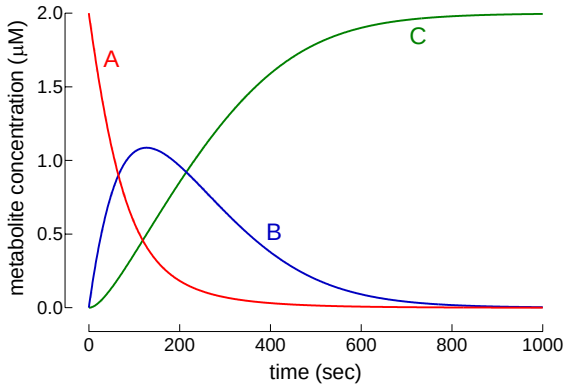

Figure 2: Metabolite production for the pathway of figure 1. In this simulation: K_A = 2 μM, $k_{c,A}$ = 50 s^{-1}, K_B = 1 μM, $k_{c,A}$ = 10 s^{-1}, and $K_{i,C}$ = 1 μM; and, $[E_1] = [E_2]$ = 1 nM, $[A]_o$ = 2 μM, and $[B]_o = [C]_o$ = 0.

that transforms it into product B. B is released from E_1 and combines with E_2 in the second step of the pathway. B serves as substrate for E_2, which catalyzes its chemical transformation into C. In this pathway, C can be seen to have a special function. C can bind to E_1, and upon binding diverts E_1 from its role as catalyst for the conversion of A into B. In this way, C exerts an inhibitory effect on the rate of the reaction catalyzed by E_1, and has the overall effect of reducing the flux through this pathway. This is a form of pathway regulation known as "feedback inhibition."[6]

When substrate A is present, the pathway depicted in figure 1 is triggered into operation. Operation of a system can be defined by the time-dependent rise and fall of the concentrations of pathway metabolites. Figure 2 is a graph of the simulated operation of the pathway depicted in figure 1. In this simulation, the system is called into action with the introduction of substrate A. As A is converted into B by the action of E_1, B begins to be converted into C by the action of E_2. As the concentration of C increases over time, it exerts its inhibitory effect and slows conversion of A to B, and B to C, thereby retarding the overall flux through the pathway. Ultimately, the concentrations of A and B fall to zero, and C rises to its maximal level.

2.3 Enzymatic Coupling and the Transition from Intracellular Pathway to bioS_{ip}

We saw in the above discussion that introduction of substrate A initiates a transformation – the enzymes and metabolites that comprise the pathway of figure 1 are transformed into a biosystem, bioS_{ip}. In remainder of this section, we will analyze this transformation in terms of the biochemical concept *enzymatic coupling*. This analysis will give us a language to speak more precisely about pathways and their biosystems and will lay the groundwork for the discussion of the next section, where we consider one of the questions that motivates this investigation: is the biosystem that is produced by such a transformation ontologically distinct from pathway components?

I begin by defining several key terms and concepts.

- An *enzyme ensemble* is an assembly of *related* enzymes.

6. Feedback inhibition is a common means by which the flux through a bioS_{ip} is regulated and involves the binding of a 'downstream' metabolite to an 'upstream' enzyme to form a complex that is catalytically inactive. The inhibition of this single enzyme retards material flux through the biosystem.

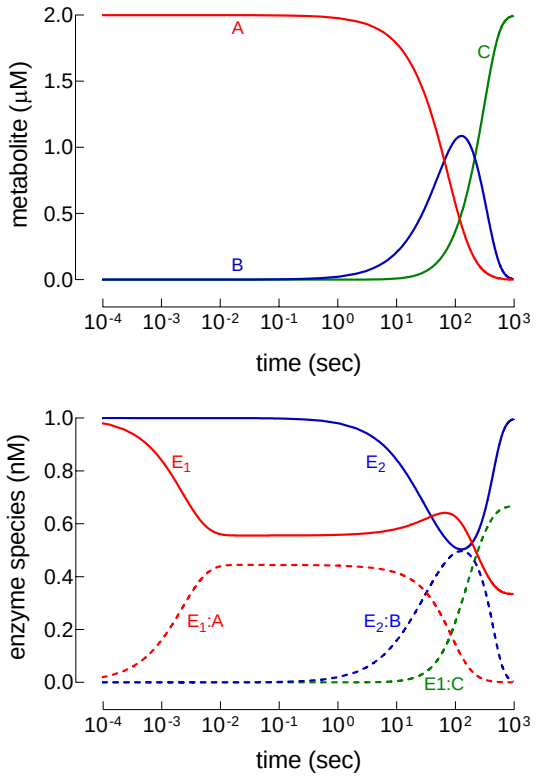

Figure 3: Time-dependencies of reaction species during enzyme ensemble coupling. Same conditions as figure 2.

- Enzymes are related if the product of one enzyme-catalyzed reaction is a substrate or a modifier[7] of another enzyme-catalyzed reaction.
- An enzyme ensemble can exist in one of two states, *quiescent* or *coupled*.
- *Coupled* is a dynamic state that exists among reactions of related enzymes. Coupling occurs upon addition of the *primary* enzyme's substrate to the *quiescent* ensemble.
- An enzyme is *primary* if its reaction is capable of initiating coupling of an ensemble to which it belongs.
- The enzymes of an uncoupled ensemble, by virtue of their being related enzymes, possess *coupling potential*.

Coupling of an ensemble of related enzymes is the transformation of the discrete components that comprise a pathway into a system of interdependent enzyme-catalyzed reactions: an assembly of related enzymes is transformed into a system of enzymes-in-relation. The biosystem that emerges from coupling mediates a catalyzed flux of starting materials to material output that cannot occur except for the coupling of pathway enzymes. Enzymatic coupling is the movement from potential to actuality; that is, the movement from potential for catalysis to system catalyst.

Coupling of an enzyme ensemble is a dynamic process that evolves through time. Consider again the pathway depicted in figure 1. In the absence of substrate A, the enzyme ensemble

7. Modifiers fall into two classes: reaction rate inhibitors or reaction rate accelerators. Both inhibitors and accelerators exert their respective effects by first binding to the enzyme to form a binary of complex of enzyme and modifier. This binary complex will have catalytic properties that are different (i.e., slower or faster) than enzyme without modifier.

comprising E_1 and E_2 is in a state of quiescence. But with the addition of A, the ensemble engages. The dynamic evolution of this biosystem is illustrated in figure 3, which graphs the temporal evolution of enzymatic coupling. In the upper panel the time courses for the production and consumption of metabolites are again illustrated, and in the lower panel the time courses for the comings and goings of the various enzyme species are drawn. Note that the time scales for these plots are logarithmic, not linear. Logarithmic time scales are necessitated by the different time domains of the various reactions that occur as this system evolves.

We see in the time courses of figure 3, that within milliseconds of the addition of A, this substrate combines with E_1 to form the complex E_1:A. At around 1 second, B begins to be produced and interacts with E_2 to form E_2:B. From this latter species, C begins to be formed. Full coupling, as defined by the state in which all the enzyme species are present, is attained at the 100 second mark and extends for perhaps a thousand seconds. Full coupling of this enzyme ensemble produces a biosystem, or $bioS_{ip}$.

During the temporal evolution of this biosystem, new entities form and then disappear. E_1 combines with substrate A or inhibitor C to form E_1:A and E_1:C, respectively, and E_2 combines with substrate B to form E_2:B. While these complexes form only transiently, during their lifetimes they are fully existent in the sense that they are no less real than the more stable species that combine to form them.[8]

This example represents a closed system (see below, section 2.4.2), and as such will evolve to a point of termination. Termination is reached, in this particular system, after about a thousand seconds when: (i) all of A has been converted, through the intermediacy of B, to C, (ii) E_1:A and E_2:B have fallen to zero, (iii) E_2 has returned to its original concentration of 1 nM, and (iv) E_1 and E_1:C are at their equilibrium concentrations, as dictated by the magnitude of $K_{i,C}$ and the final concentration of C.

2.4 Systems in Nature: Integrated and Open

The pathway that is depicted in figure 1, while accurately portrayed in its operation in figures 2 and 3, is an unrealistic abstraction of biosystems that exist in nature in that it lacks environmental context. Unlike this system, $bioS_{ip}$s in cells do not exist isolated and closed; rather they are integrated into a complex matrix and open to material transfer. In the remainder of this section, I will discuss the two concepts of biosystem integration and openness.[9]

2.4.1 $bioS_{Ip}$S Are Integrated Into Their Cellular Environment

Figure 4 illustrates how the pathway of figure 1 might be integrated with another $bioS_{ip}$, and thus participate in the broader physiology of a cell. Two modes of integration are depicted: sharing of an enzyme by two $bioS_{ip}$s, and involvement of a metabolite in two $bioS_{ip}$s. Enzyme sharing, from the perspective of the linear pathway A→B→C→D, reduces the effective concentration of the enzyme that converts B into C, which has the effect of slowing this reaction.

8. This analysis assumes an ontological antireductionist stance in which molecular entities are actual. This position has been defended previously (Stein 2004; 2006; 2008) and will be again considered later in this paper.

9. One of the reviewers of this paper asked whether, given the open nature of $bioS_{ip}$s and the level of their integration into larger biochemical networks, we should question their existence as actual entities. This is at once a question of biological practice and metaphysical ontology. Biologists and biochemists clearly accept the existence of $bioS_{ip}$s, as evidenced by reference to any textbook of introductory biochemistry, the growing literature on the evolution of metabolic pathways (Fani 2012), and metabolic tracer experiments (Allen and Young 2020). The metaphysical question is of course a species of the broader question of individuality – in the radically interconnected world in which we live, how can we justify singling out anything as an individual? It is, of course, precisely the narrower biological question that I address in this paper.

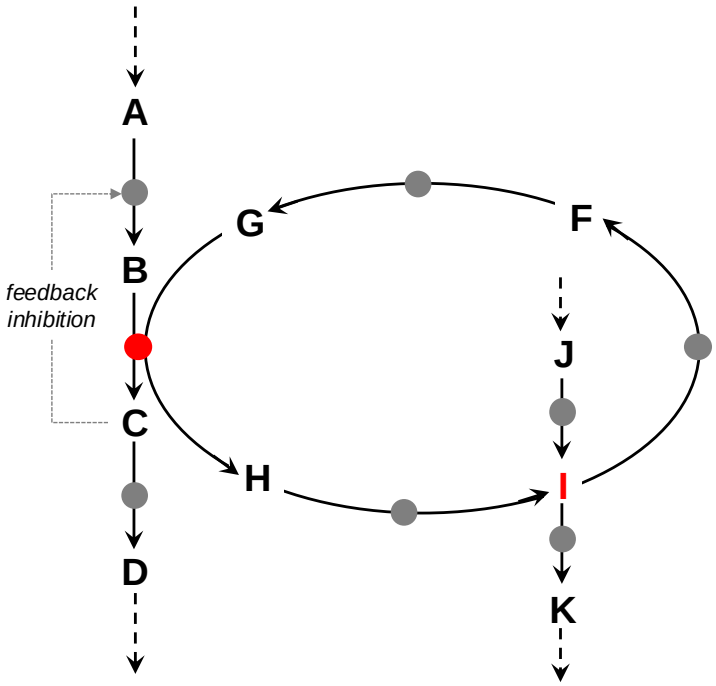

Figure 4: Systems integration. Integration of the linear pathway of figure 1 with another pathway. Solid arrows represent enzyme catalyzed reactions; enzymes are depicted as grey circles. Dashed arrows are the production or consumption of metabolites by other bioS_{ip}s.

This would have an impact both on the feedback inhibition of the pathway and on overall flux through the pathway. Involvement of metabolite I in the linear pathway J→I→K, reduces the concentration of I that is available to be transformed into F, thus reducing the flux through the circular pathway.

bioS_{ip}s are deeply integrated into their environment, and are responsive to environmental perturbation. The environmental sensitivity of bioS_{ip}s has its origins in the environmental sensitivity and responsiveness of each of the enzymatic reactions that comprise the biosystem. Enzymes can detect changes in pH, ionic composition, and concentration of certain metabolites via both specific and non-specific binding interactions. Due to the dynamic nature of internal enzyme structure, these binding events can be transduced into changes in reaction rates of the reactions they catalyze. Like enzymes, certain metabolites, particularly those with complex structures (e.g., RNA), can also detect and respond to environmental changes. In complex biosystems that are the product of evolutionary pressures, the system would respond to environmental perturbations in a manner that works to maintain homeostasis of the broader cellular system of which it is a part.

2.4.2 bioS_{ip}s Are Open

As described in the previous subsection, operation of the pathway depicted in figure 1 generates a materially closed system, meaning that after initiation of the system by addition of substrate A, no system components are introduced or removed. Metabolites rise and fall due entirely to operation of the system itself.

In the context of a living cell, such a situation never occurs because bioS_{ip}s are open, with all of their components generated or consumed by other bioS_{ip}s of the cell. For linear pathways,

such as the one depicted in figure 1, initiating substrates (A in figure 1) are constantly produced by other bioS_{ip}s, and terminal metabolites (C in figure 1) do not accumulate, but are consumed by other bioS_{ip}s. In addition, the component enzymes of bioS_{ip}s are themselves both products of protein biosynthetic systems and substrates for degradative systems, which work to regulate the concentrations of these enzymes.

3 Ontological Status of bioS_{ip}s

In the previous section we saw that coupling of the enzyme components of a pathway to form a biosystem is a transition from potentiality to actuality. In this section we will explore whether this transformation represents a change in ontological status: is the system that results from enzymatic coupling ontologically distinct from the pre-transformation ensemble of related enzymes? And, if so, what is the ontological status of post-transformation bioS_{ip}s?

I'll attempt to answer these questions with the analyses contained in the next four subsections. In the first subsection, I'll increase the precision of our discussion by introducing and carefully defining two terms – *functional whole* and *actuality*. Next, in section 3.2, I'll consider the ontological significance of a bioS_{ip}, where I propose that ontological significance is grounded in causal efficacy. Here, I'll argue that the biosystem that emerges from the coupling of an enzyme ensemble is ontologically significant. Next, in section 3.3, I'll suggest that there are degrees of ontological significance, and establish criteria for assessing degrees of ontological significance based on a parameter I call *biosystem complexity*, which increases with the density of internal interactions and the breadth of external interactions. Based on this, I argue for a hierarchy of ontological significance that increases from an assemblage of unrelated enzymes to bioS_{org}s. Finally, in section 3.4, I ask if bioS_{ip}s are actualities. The key question here is this: how can a bioS_{ip}, comprising discrete enzymes and metabolites, be anything more than a collection of these parts?

To increase the biological relevance of our discussion, I broaden our focus from the simple, hypothetical pathway of figure 1 to the glycolytic pathway of figure 5. Glycolysis, a critically important metabolic pathway in both prokaryotes and eukaryotes, produces energy rich molecules from the foodstuff glucose. The glycolytic pathway comprises ten enzymes as well as the initiating substrate glucose and secondary metabolites ATP, ADP, NAD^+, and NADH. In the absence of glucose, the glycolytic enzymes of figure 5 exist as a quiescent ensemble of related enzymes. But upon introduction of glucose and auxiliary substrates NAD^+, ATP, and ADP, the ensemble undergoes coupling to produce the fully functional glycolytic bioS_{ip}.

3.1 Biosystems Complexity

In the next subsections, I'll spend considerable time discussing complexity and how it contributes to and defines the ontological significance of biosystems. Given this, it seems appropriate to first try to describe what I take biosystems complexity to mean.

Anyone who has spent any time trying to find a definition of complexity from the writings of complexity theorists will come away from these efforts disappointed. Maria Kaiser (2013, 456) explains that although complexity plays center stage in several research fields, "there exists neither a unified science of complex systems nor a consensus about what complexity is and what makes a system complex. Rather, the characterizations of complexity partially vary from field to field and from author to author." There seem to be as many definitions of complexity as there are complexity theorists.

Ladyman, Lambert, and Wiesner (2013), after reviewing various attempts in the literature

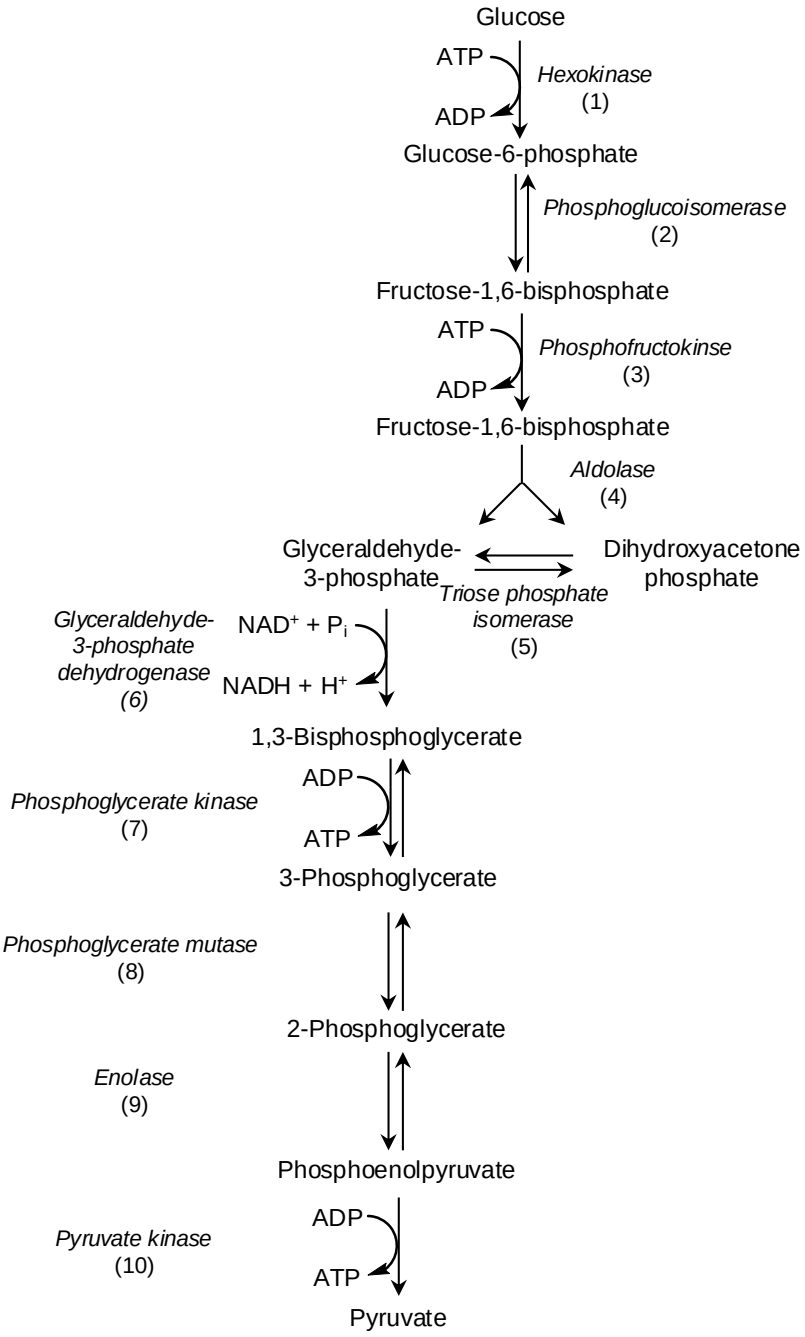

Figure 5: The glycolytic bioS_{ip} coverts glucose into pyruvate. Steps 1 and 3 consume ATP and steps 7 and 10 produce ATP. Since steps 6–10 occur twice per glucose molecule, there is a net production of ATP.

to characterize complex systems, offer a list of necessary conditions a system must meet to justify the characterization of being complex. They conclude that a complex system comprises an ensemble of many elements that interact in such a way as to bring forth a "robust order" from apparent disorder. Estrada Ernesto, in the abstract to a recent paper, offers this succinct definition:

> a complex system is defined as a system where there is a bidirectional non-separability between the identities of the parts and the identity of the whole. Thus, not only the identity of the whole is determined by the constituent parts, but also the identity of the parts are determined by the whole due to nature of their interactions. (Estrada 2023)

Another defining aspect of biosystems complexity is their hierarchical nature and the integration among the various levels of the hierarchy. This was recognized as an important aspect of biology as early as 1945, when Alex Novikoff wrote:

> What were wholes on one level become parts on a higher one. Each level of organization possesses unique properties of structure and behavior which, though dependent on the properties of the constituent elements, appear only when these elements are combined in the new system… The parts and wholes are material entities and integration results from the interaction of the parts, as a consequence of their properties. (Novikoff 1945, 209)

The concept of biosystems complexity that underpins this work draws on these descriptions. I define a complex biosystem as an ensemble of biochemical entities (e.g., proteins and metabolites) that are organized in such a way as to allow interaction among these entities to produce a phenomenon. Different hierarchical levels may exist in this ensemble, in which case both inter-level and intra-level interactions will exist. And finally, different gradations of complexity can exist (see section 3.4).

3.2 Functional Wholes vs. Actualities

An actuality designates a physical entity that stands identifiably apart from its environment, and has an integrated internal complexity that allows it to interact with its environment and to operate as a unit within its environment. Actualities can be said to possess an ontological unity. Actualities include living humans and cats, as well as single-celled organisms such as amoebas, and non-living entities such as molecules and atoms, whereas bales of hay, piles of bricks, dead cats, and chairs are not actualities. Functional wholes are similar to actualities in that they respond to environmental perturbation as a whole, but they do not stand apart from their environment. The unity that both actualities and functional wholes possess is discovered through scientific investigation; to say something exists in the world as a unity, whether it be an actuality or functional whole, is to say something about that thing's behavior.

Of course, there will be some degree of vagueness in this discussion. Consider the variety of assemblies of plants and animals that exist in nature. The random collection of plants I have on my patio together with the squirrels running through the trees clearly do not constitute a functional whole, much less than an actuality. But what about a woodland ecosystem? While I think one could successfully argue for a woodland being a functional whole, the diffuse boundary separating it from surrounding grasslands would likely disqualify it from rising to the status of an actuality. But perhaps not so for a small, tropical island ecosystem. Here a more clearly

defined boundary (i.e., shoreline) may allow it to rightfully be considered an actuality. The vagueness that is apparent here should not disturb us, though. As David Odenberg points out, citing Samuel Johnson, "the existence of twilight does not mean we cannot distinguish between day and night" (Oderberg 2017, 216).

3.3 Ontological Significance of the Coupled Enzyme Ensemble

We saw in section 2 that the transition from pathway to $bioS_{ip}$ represents a change of state from quiescence to activity. The question I consider in this subsection is whether ontologically significant consequences attend this change.

A criterion that can be used to assess the ontological significance of an entity was proposed by David Armstrong, who suggested that the ontological significance of an entity is related to its causal efficacy. He postulated that everything we take "to exist should make some sort of contribution to the causal order of the world" (Armstrong 2004, 37). Armstrong called this the Eleatic Principle, after a passage from Plato's Sophist, in which the Eleatic Stranger suggests that causal power is the mark of being. Now, when considering an entity comprising parts, chemist and process philosopher Joseph Early advises that we make use of what he dubbed the *Extended* Eleatic Principle:

> **EEP** The Extended Eleatic Principle asserts that each ontologically significant entity must, somehow or other, exert causal influence that is not simply reducible to the causality of the components. (Earley 2008, 183)

While Earley does not define "causal influence" or describe how he assesses a thing's reducibility relative to its component parts, I think we can rephrase his Extended Eleatic Principle, and still stay true to Earley's intent:

> **EEP*** An entity has ontological significance if it possesses defining characteristics that are not possessed or cannot be manifested by any one of its component parts, or combination of a subset of component parts.

The glycolytic $bioS_{ip}$ has two system-level defining characteristics: (i) it is a catalyst for the production of energy-rich NADH and ATP from glucose, and (ii) the flux through the system is regulated by environmental factors.[10] Significantly, none of the component enzymes of the glycolytic pathway or subset of component enzymes can manifest these defining characteristics.

The conclusion that we can draw from this analysis is the glycolytic $bioS_{ip}$, or indeed any $bioS_{ip}$, is, in fact, ontologically significant, given that its defining characteristic of environmentally regulated system catalyst is not possessed by the enzymes of the ensemble that gave rise to it.

10. As elucidated by Berg, Tymoczko, and Styer:

> The rate of conversion of glucose into pyruvate is regulated to meet two major cellular needs: (1) the production of ATP generated by the degradation of glucose, and (2) the provision of building blocks for synthetic reactions, such as the formation of fatty acids. In metabolic pathways, enzymes catalyzing essentially irreversible reactions are potential sites of control. In glycolysis, the reactions catalyzed by hexokinase, phosphofructokinase, and pyruvate kinase are virtually irreversible; hence, these enzymes would be expected to have regulatory as well as catalytic roles. In fact, each of them serves as a control site. Their activities are regulated by the reversible binding of allosteric effectors or by covalent modification. (Berg, Tymoczko, and Styer 2019)

While these interactions occur at the level of specific enzymes of the biosystem, they evolved to fine-tune the flux through the glycolytic $bioS_{ip}$ and not to simply regulate the activity of a single enzyme.

3.4 Degrees of Ontological Significance

I wish to now consider the proposition that there are *degrees* of ontological significance among biosystems, and that the degree of ontological significance is related to its casual efficacy and can be assessed based on a feature I refer to as *biosystem complexity*. I take biosystem complexity to increase as two factors increase: density of internal interactions and breadth of external interactions.[11]

Density of internal interactions is a measure of the number and frequency of interactions among the elements that comprise the biosystem. For a $bioS_{ip}$, these elements are subordinate $bioS_{ip}$s and enzymes, while for a $bioS_{cell}$, these elements are a complex hierarchy of $bioS_{ip}$s that are enumerated first at the level of systems that are immediately subordinate. These systems will have their own subordinate systems, and these perhaps other subsystems. For $bioS_{cell}$s, systems nesting occurs all the way down to individual enzymatic reactions. All of these nested processes contribute to the density of internal interactions. The frequency of internal interactions is a composite factor that depends on the rates of the flux through each of these nested processes. For $bioS_{ip}$s, the frequency of internal interactions is related to the rates of each of the enzymatic reactions that comprise the $bioS_{ip}$ and dynamical fluctuations of the enzymes of the $bioS_{ip}$. For $bioS_{cell}$s, the frequency of internal interactions is dependent on the dynamics of major $bioS_{ip}$s (e.g., protein synthesis and gene expression) and then on the hierarchy of subordinate $bioS_{ip}$s that define each of these. For both $bioS_{ip}$s and $bioS_{cell}$s, their defining processes occur on very different time scales that range from nanoseconds to seconds. Frequency of internal interactions is a function of all these temporally disparate, yet hierarchically nested, processes.

Breadth of external interactions is a measure of the number and type of external interactions. Considering first $bioS_{ip}$s, recall that they not only interact with other $bioS_{ip}$s (see figure 4), but also with many different types of elements in their environment, such as metal ions, allosteric modulators, and proteins. External interactions of $bioS_{ip}$s are initiated at the level of the individual enzymes of the system, but then propagate through the system. External interactions of high-order biosystems, such as a $bioS_{cell}$, rely on cell-surface receptors, or sensors, which are integrated into the internal workings of a cell through intricate signal transduction pathways. Breadth, for both $bioS_{ip}$s and $bioS_{cell}$s, refers to the number and sorts of stimuli that can be sensed by these systems.

As the depth of internal interactions and breadth of external interactions increase, the biosystem will be able to respond to environmental perturbation in novel ways, that is, manifesting responses to environmental perturbation that could not occur were it not for the interactions. Complex $bioS_{ip}$s will exhibit greater sensitivity to feedback inhibitors and will show self-correcting behavior in the face of deleterious environmental factors. High order biosystems, such as $bioS_{cell}$s or $bioS_{org}$s, will respond to changing environmental conditions through mechanisms that result in adaptive stabilization or perhaps even adaptive self-organization, which would trigger transformation to a new biosystem (Laszlo 1972). In addition, as an extension of Armstrong's (2004, 37) Eleatic Principle, we recognize that with increased complexity comes greater contributions to the causal structure of the world. This occurs through a greater scope of interactions and increased ability to respond to the world. Finally, increased complexity leads to an enhanced recalcitrance to reduction to the operation of underlying systems. All this points to a greater ontological significance for more complex entities.

From the preceding discussion, we see that a quiescent enzyme ensemble that defines an

11. As the reader will likely recognize, this analysis has the potential to be developed in a more quantitative, mathematical fashion. However, this is beyond the scope of the current paper. For our purposes here, a qualitative approach will suffice.

intracellular pathway has minimal ontological significance. The ontological significance it does possess is due to the related nature of the enzymes that comprise the ensemble, and thus the system-catalyst potentiality possessed by the ensemble. Clearly, a set of unrelated enzymes entirely lacks such potentiality and is ontologically insignificant.

What if we move outward from $bioS_{ip}$s to higher ground, to a position that allows a view encompassing the totality of a cell's physiology? From this perspective, what can we say about the ontological significance of a cell relative to the ontological significances of each of its many constitutive $bioS_{ip}$s? From the foregoing discussion, we conclude a $bioS_{cell}$ has greater ontological significance than a $bioS_{ip}$, and further, that we are justified in constructing the following hierarchy of ontological significance:

$$\text{unrelated enzymes} < \text{related enzymes} < bioS_{ip} < bioS_{cell} < bioS_{org}$$

3.5 Ontological Status of Biosystems: Are $bioS_{ip}$s Actualities?

In the previous two subsections, I first argued that a $bioS_{ip}$ is ontologically significant by virtue of possessing causal efficacy beyond that of its component enzymes, and then, by reason of its biosystem complexity, that it has an ontological significance greater than the ontological significance of its pre-coupled enzyme ensemble. The final question I wish to address in this section is whether a $bioS_{ip}$ is an actuality, or whether, despite its ontological significance, it has an ontological status that does not rise to this level.

Among the physical entities that the biological sciences might count as actualities are cells. However, if a convincing argument is to be made for the cell existing as a unified whole, one must explain how a cell can simultaneously comprise parts and yet be a whole. Any argument for the organismic unity of the cell must counter the findings of over a century of biochemistry and decades of molecular biology that have taught us that the cell is an intricate machine comprising a complex assembly of proteins, nucleic acids, and metabolites. Despite these findings, I will argue for the organismic unity of the cell, and will propose that this unity is not only compatible with, but is, in fact, grounded in the mechanistic understanding of the cell that has been revealed to us by biochemistry and molecular biology.[12]

Consider the dramatic effects of insulin on the physiology of a mammalian cell, say a hepatocyte. When a hepatocyte is exposed to insulin, the hepatocyte responds by increasing its uptake of glucose, decreasing *de novo* synthesis of glucose, and increasing synthesis of fatty acids and proteins. The hepatocyte responds as a whole to insulin by suppressing flux through the critical metabolic processes of glycogenolysis and gluconeogenesis. We, of course, now understand the molecular basis for the hepatocyte's response to insulin. The observed phenomena occur

12. The concept that the unity of an actuality, and other complex systems, is grounded in mechanistic understanding was inspired by Errol Harris' (1965; 1970) account of teleology, who explains that teleology is best viewed as a system's potentiality or built-in directionality, not as the end somehow dictating the present. The teleological aim that is possessed by complex systems "in no sense excludes or contradicts mechanics or violates physio-chemical laws, for it is by their means alone that the adjustment or parts and variation of activities is effected" (Harris 1965, 278). As with teleology, mechanism also grounds ontological unity. In a recent book chapter, Stuart Glennan (2024) tells us that the mechanisms operating within a complex system cause the emergent properties that define that system. He explains that "whenever some emergent phenomenon occurs, there is a mechanism responsible for its emergence" (Glennan 2024, 213), and goes on to say that "the basic supposition of a mechanistic theory of emergence is that emergent phenomena emerge out of the activities of mechanisms" (Glennan 2024, 215). Similarly, William Wimsatt expresses the idea that "emergent phenomena are often subject to surprising and revealing reductionistic explanations. But giving such an explanation does not deny their importance or make them any less emergent – quite the contrary; it explains why and how they are important… *A reductive explanation of a behavior or a property of a system is one that shows it to mechanistically explicable in terms of the properties and interactions among the parts of the system*" (Wimsatt 2007, 275; Wimsatt's italics).

as a result of insulin molecules binding to specific receptors on the outer surface of the cell, thereby triggering a cascade of enzyme-mediated reactions that propagates throughout the entire cell, ultimately causing these physiological effects. The critical feature here is that because of the global integration of intracellular processes, the hepatocyte's response to insulin does not remain local, at the level of cell surface receptors, but propagates throughout the entire cell, ultimately effecting the overall physiology of the cell. Thus, our understanding of the cell as an organismic unity does not exclude or contradict mechanistic understanding; rather, mechanism grounds organismic unity and explains how it arises.

Returning now to bioS_{ip}s, recall that in previous sections of this paper I argued that bioS_{ip}s respond to environmental perturbation as unities. I supported this assertion by citing the malleable behavior of bioS_{ip}s in the face of a changing environment – raise or lower the pH, ionic strength, or concentration of a feedback inhibitor, and flux through the entire bioS_{ip} will be altered. One might counter this argument by pointing out that any environmental change that modulates the behavior of a bioS_{ip} will initially be at the level of a particular pathway enzyme. While this is undeniably true, I do not believe it detracts from the argument that bioS_{ip}s operate as wholes – it simply elucidates the mechanism by which modulation of the biosystem's holistic behavior occurs. The mechanism we saw above for the effect of insulin on hepatocytes is analogous to that which occurs when a perturbant, say a feedback inhibitor, binds to one of the enzymes of a metabolic pathway and alters behavior of the bioS_{ip} as a whole; that is, binding of the inhibitor to its enzyme initiates a local event that ultimately propagates through the entire bioS_{ip}.

Existing in the world as a functional whole increases the ontological significance of an enzyme ensemble to that of a bioS_{ip}. But to exist in the world as an actuality, this system must also stand identifiable apart from its environment. For a physical entity to be distinct from its environment, the entity must have structural integrity and compositional definiteness. Cells, such as hepatocytes, and single celled organisms, such as paramecia, possess these properties and stand distinct from their environment because of their cell membranes, which act not only as a delimiting boundary between interior and exterior, but also as a translocational barrier that tightly regulates internal composition. But is this so for bioS_{ip}s? The more a bioS_{ip} lacks structural integrity and compositional definiteness, the more questionable is its individuation and thus its status as an actuality.

The once common notion that a cell is a simple "bag of proteins" supports the view that bioS_{ip}s lack individuation. Under such a view of a homogenous cell interior, the enzymes of the pathways that give rise to bioS_{ip}s are dispersed randomly throughout the cytoplasm. It is difficult to see how bioS_{ip}s such as these could be considered individuated.

But, of course, this view of an undifferentiated cytoplasm is incorrect. The interior of eukaryotic cells, as well as prokaryotic cells, are highly structured. Not only do these cells contain numerous types of organelles and complex supramolecular assemblies (e.g., ribosomes and proteosomes), they are also internally structured by cytoskeletal proteins. It has been proposed that one of the roles of the cytoskeleton is to serve as scaffold for the spatial organization of the enzymes of metabolic pathways (Araiza-Olivera et al. 2013; Cohen and Pielak 2017; Kastritis and Gavin 2018; Skalidis, Tüting, and Kastritis 2020). These assemblies are called *metabolons*, a term coined in 1985 by biochemist Paul Srere to designate a "supramolecular complex of sequential metabolic enzymes and cellular structural elements" (Srere 1985).[13] Dozens of bioS_{ip}s have been proposed to exist as metabolons or similarly ordered structures of enzymes, and may

13. The organization of the enzymes of a metabolic pathway into structural units had been proposed previously, and may have been first conceived in 1970 by A. M. Kuzin of the USSR Academy of Sciences (cited in Lyubarev and Kurganov 1989).

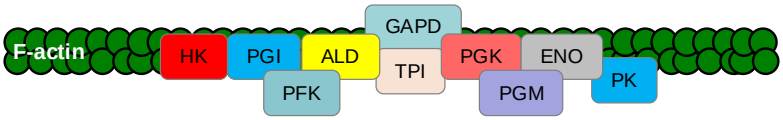

Figure 6: Depiction of the glycolytic metabolon, where enzymes are scaffolded on F-actin and interact with one another to facilitate shuttling of intermediates from active site to active site. Such a structure represents a classical metabolon which incorporates a full metabolic pathway. (Araiza-Olivera et al. 2013)

represent the primary way bioS_{ip}s operate in nature (Dahmani et al. 2023; Kastritis and Gavin 2018; Kondrat and von Lieres 2022; Pedley, Pareek, and Benkovic 2022; Tian, Fan, and Elf 2021).

The glycolytic bioS_{ip} we previously discussed is thought to exist as a metabolon. Figure 6 depicts the glycolytic metabolon as described by Salvador Uribe Carvajal and coworkers (Araiza-Olivera et al. 2013). The authors explain in the paper's abstract that in brewer's yeast *Saccharomyces cerevisiae*, "polymeric filamentous F-actin … stabilizes both the interaction of isolated glycolytic pathway enzymes and the whole fermentation pathway, leading to higher fermentation activity."

The structure of the metabolon facilitates metabolite flux through and environmental responsiveness of the bioS_{ip} (Sweetlove and Fernie 2018). And, significantly for the ontological argument being made here, structure sets the bioS_{ip} apart from its environment and gives it compositional definiteness.

Given these arguments, I believe we are justified in concluding that the subset of bioS_{ip}s that exist as metabolons (hereafter referred to as bioS_{ipm}s) are actualities.[14] bioS_{ip}s that lack the structural integrity, compositional definiteness, and individuation afforded by existing as a metabolon, while ontologically significant and still possessing functional unity, cannot rightly be classified as actualities.

4 Metaphysical Foundations for the Ontological Unity of Actualities

We saw in previous sections that certain assemblies of enzymes can undergo a process of coupling in which they are transformed from an ensemble of related enzymes into a system of enzymes-in-relation. They become a functional whole. An additional level of organization is available to such systems. Here, they are organized spatially within the cell as an individuated entity to optimize material flux through the system. These are metabolons, and exist as actualities.

In this section, I'll explore the metaphysical foundations that underpin the unity of these entities. What I am fundamentally asking is this: what must the world be like for the emergence of actualities? Three metaphysical systems will help us here: process philosophy, Aristotelian-Scholastic substance metaphysics, and Ivor Leclerc's philosophy of nature. Critically, these systems all regard nature as inherently dynamic and relational, and it is these features of reality that will ultimately allow us to explain the unity of biological systems that exist as actualities.

14. A reviewer of this manuscript rightly pointed out that 'actuality' is a broad category encompassing functional wholes ranging from metabolons, to cells, to multicellular organisms, to humans, each comprising increasingly greater degrees of "systemic functional autonomy," as the reviewer referred to it. The reviewer went on to suggest that in light of this, it would useful to introduce and define degrees or distinct levels of actuality. While this may be helpful, it is a project beyond the scope of this manuscript, and constitutes an interesting project in itself.

4.1 Process Philosophy

Process philosophy offers us a view of the world in which becoming is ontologically more fundamental than being. Stability is an illusion and change is the only constant. The actualities of this world are dynamic entities with temporal evolutions that depend on relational interaction with other actualities.

Process ontology opposes the substance ontology of the early modern era of philosophy, which viewed substances as static, elemental particles with no interior natures, and the change of complex entities as the mechanical rearrangement of these elemental particles. The observations of contemporary science are at odds with such views. Both the biological and molecular sciences describe a world of relational dynamism, in which properties of molecules and organisms are never static and must always be viewed in the context of their environment. The tenets of process philosophy have been shown to provide strong metaphysical support to the findings of chemistry (Kopel 2019; Stein 2004), biochemistry (Alassia 2022; Guttinger 2018; 2021; Stein 2004; 2006; 2022), and biology (Dupré and Nicholson 2018; Dupré 2020).

However, process philosophers are divided on whether biological entities, such organisms, cells, and molecules, are, in fact, ontological unities. In Alfred North Whitehead's philosophy of organism (Whitehead [1925] 1967, [1929] 1978, [1933] 1967), complex entities and the things of common experience are groupings, or 'societies', of actual entities. Whitehead tells us that the "real things that endure are all societies" (Whitehead [1933] 1967, 204). Thus, it is societies of actual entities that comprise our world, and nature exists as systems of nested societies. "The Universe achieves its values by reason of its coordination into societies of societies, and into societies of societies of societies" (Whitehead [1933] 1967, 206). Thus, the things of everyday life and scientific investigation are only derivatively actual. Such an ontology has been countered by process philosophers who regard all living entities, and perhaps some complex non-living entities (e.g., molecules and atoms), as fully actual ontological unities (Cobb 1965; 1984; Earley 1981; Felt 2001; Griffin 1988; Wallack 1980).

These philosophers, while still working within a largely Whiteheadian tradition, see the actualities of the world as ontological unities. But how do they account for this unity? In answer to this, Charles Hartshorn developed the concept of the 'compound individual' as an enduring existent comprising a 'society' of interlocked individuals (Hartshorne 1936). David Griffin gives a clear definition: "Certain combinations of enduring individuals allow for the emergence of higher-level individuals, with the resulting totality being what Hartshorne has called a"compound individual" (Griffin 1997, 264). While the most obvious examples of compound individuals are animals, the part-whole relationship of the compound individual applies to any entity which responds as a whole to its environment. Thus, single-celled organisms, the organelles of cells, macromolecules and simple molecules are all compound individuals. In compound individuals, ontological unity results from the emergence of a synthesizing dominating unit, much like Leibniz's 'dominant monad'.

The ontological unity of actualities can also be explained by process ontological approaches outside of the Whiteheadian tradition. John Dupré and Daniel Nicholson, in their "Manifesto for a Processual Philosophy of Biology," explain that biological entities can be envisioned as processes within process, or as Rescher expressed: "processual particulars are systemic wholes comprised of subordinate processes in ways that factor 'all the way down'" (Rescher 1996, 55).

> At no level in the biological hierarchy do we find entities with hard boundaries and a fixed repertoire of properties. Instead, both organisms and their parts are exquisitely regulated conglomerates of nested streams of matter and energy. The processes that make up the biological hierarchy not only compose one another but

> also provide many of the enabling conditions for the persistence of other processes in the hierarchy, at both higher and lower levels. In other words, the visible and tangible entities at each level are not simply given (as they are in a structural hierarchy of things), but are rather dynamically maintained by continuous activity taking place at higher and lower levels in the same hierarchy. (Dupré and Nicholson 2018, 27)

4.2 Aristotelian-Scholastic Substance Philosophy

Substance philosophy of the classical Aristotelian-Scholastic tradition, like certain strands of process philosophy, sees the actualities of the world, or 'substances', as ontological unities. The challenge facing Aristotelian-Scholastic philosophers is the same as that faced by these process philosophers – how to account for this unity. In this section, I outline such an account, starting with the view of substance as seen in the Aristotelian-Scholastic tradition.

As noted above, the development of process philosophy was in large part motivated by perceived metaphysical inadequacies of the ontologies of early modern philosophers, such as Descartes and Locke, that conceive substances as static, elemental particles that are mechanically arranged to constitute the actualities of the world. However, this in no way represents the classical view of substance.[15]

Misunderstanding perhaps begins with the translation of Aristotle's *ousia*. It has been argued that *ousia* is best translated not as substance, but as "physical entity" (Sfekas 1991, 40). *Ousiai* include not only horses and men, as exemplified in Aristotle's *Categories*, but also, as pointed out by W. Norris Clarke (2001, 65), single celled organisms and non-living entities, such as molecules and atoms.

The assumed static nature of Aristotelian substances has also been refuted. Leonard Eslick argues that "it is a travesty to depict Aristotle's substance as static and inert, hermetically sealed off from the causal efficacy of other entities, and devoid of any internal becoming" (Eslick 1958, 504). Stanley Sfekas echoes these thoughts, maintaining that "the notion of substance as a characterless substrate is an absurd one, and Aristotle never held such a notion… [Substance] is defined precisely as that which undergoes change … a pattern of novelty that emerges in process" (Sfekas 1991, 32, my italics).

Perhaps the most fully developed arguments for the dynamic and relational nature of the Aristotelian concept of substance have come from W. Norris Clarke, who explains that the classical, pre-Cartesian notion of substance is one of dynamism and relation, where substance is "an abiding center of acting and being acted upon [with] relations as an intrinsic dimension of being" (Clarke 1993, 164). And that "the intrinsic structure of all being is irreducible dyadic: *substance-in-relation*… *To be* in the world of real existents is to be *substance-in-relation*" (Clarke 1993, 174–75, his italics).

A defining feature of a 'substance' is its ontological unity. Clarke explains that "ontological unity as a property of being signifies the inner cohesion of something by which it constitutes an

15. W. Norris Clarke explains that

> the classical notion of substance as active nature imbedded in a network of relations resulting from its acting and being acted upon has been gradually distorted in successive stages throughout the history of post-Cartesian thought. I like to call this chapter in the history of substance: 'The Sad Adventures of Substance in Modern Philosophy from Descartes to Whitehead'… The three successive stages of this distortion can be summed up as (1) the Cartesian self-enclosed substance; (2) the Lockean inert substance as unknowable substratum; and (3) the Humean separable substance, rejected as unintelligible. (Clarke 1993, 164)

undivided whole… It coheres together within itself as a single undivided whole" (Clarke 2001, 61). But how is this unity attained?

The solution to this problem, according to Thomistic tradition, is *virtual being*. To help understand this concept, we can turn to chemistry. Consider the molecule. Chemistry tells us that a molecule is a group of atoms that are bonded together and represents the fundamental unit of a chemical compound that can take part in a chemical reaction. In Aristotelian-Scholastic tradition, a molecule is an example of a substance, an ontological unity whose properties cannot be reduced to those of its constituent atoms. How can this be? While it cannot be denied that a molecule is composed of atoms, Aristotelian-Scholastic philosophers would insist that those atoms do not exist in the molecule *actually*, but only *virtually*. Importantly, the claim is not that the atoms do not exist in the molecule, but rather that they do not exist in the molecule in the way that they exist when they exist on their own in elemental form (Feser 2019, 27). The fact that the molecule has properties that its constituent atoms do not supports the view that a molecule cannot be reduced to a sum of its parts. By the same token, the molecule lacks properties that the atoms in their elemental form possess. This is, of course, just what we would expect if the atoms are in the molecule in the sense that a hylomorphic analysis would imply, i.e., virtually rather than actually (Feser 2019, 335). David Oderberg illustrates these points using water as an example:

> If water contained actual hydrogen, we should be able to burn it – but in fact the opposite is the case. If the water contained actual oxygen, it should boil at -180°C – but in fact it boils at +100°C. Of course, the response is that the oxygen and hydrogen are bonded in water and so cannot do what they do in the absence of such a bond. But that is precisely the point. The combustibility of hydrogen and the specific boiling point of oxygen are properties of those elements in the technical [Aristotelian] essentialist sense – they are accidents that necessarily flow from their very essence. Since those properties are absent in water, we can infer back to the absence of the essences from which they necessarily flow. Therefore, neither hydrogen nor oxygen is actually present in water. Rather, they are virtually present in the water in the sense that some (but not all) of the powers of hydrogen and oxygen are present in the water… (Oderberg 2007, 75)

The functional wholeness that a molecule possesses is an empirical property; a property open to experimental verification. This wholeness manifests as a set of essential properties – what it is to be this sort of molecule rather than another sort of molecule. In the Aristotelian-Scholastic tradition, a molecule would be said to possess an ontological unity and essential properties by virtue of being a substance.

A similar explanation has been offered by David Oderberg (2017) in the context of biological organisms. Oderberg explains that *form* is the unifier of the organism, where "forms are universal determining principles whereby things are endowed with substantial natures and accidental characteristics" (Oderberg 2017, 213). Substantial form "is a metaphysical posit not the subject of an empirical hypothesis… It is what we *must* have if unity is to be explained" (Oderberg 2017, 229). Form is metaphysically responsible for a substance having a certain nature.

Oderberg explains that the organs of an organism, like the atoms of a molecule, do not have their own substantial form, for if they did, they would be substances (Oderberg 2017, 219). Although the organ does not have its own substantial form, it is united to the whole by the substantial form that makes the organ a whole, a unity.

4.3 Ivor Leclerc's Philosophy of Nature

Ivor Leclerc, in "The Nature of Physical Existence" (1972) and his later work "The Philosophy of Nature" (1986), sought to explain the nature of the physical entities that populate the universe. While these ontological studies draw heavily on Aristotelian metaphysics and Whiteheadian process philosophy, he was dissatisfied with both. In the Aristotelian-Scholastic tradition, complex entities that comprise parts exist fully actually as substances, but their parts have no claim to true actuality. In Whitehead's process philosophy, the inverse is the true nature of reality; complex entities are ontologically derivative, merely 'societies' of actual entities. Leclerc saw both accounts as only partially correct; the chief task of his work was to develop a coherent ontology in which both complex entities and their parts exist as fully actual.

In "The Nature of Physical Existence," Leclerc solved this problem with the development of the "compound substance." He starts with the premise that "crucial to the concept of substance is unity" (Leclerc 1972, 297), maintaining that "atoms, molecules, and cells very clearly are not mere aggregates; they are each unitary compounds, of a very definite order and structure, exhibiting a specific character and behavior" (Leclerc 1972, 309). The chief means by which unity of compounds is achieved is through a reciprocal acting, or becoming, of the constituent entities of a complex substance:

> The entities in relation act on each other reciprocally, and are thus each modified, in some respect, by the relationship, that is, by the acting. This reciprocal acting constitutes a tie or bond between them, this bond being the relation – which exists only in the acting… This means that by virtue of the mutual activity of relating, there exists a form or character common to the entities acting. (Leclerc 1972, 309–10)

Later, in "The Philosophy of Nature," a similar ontology is developed, but now Leclerc refers to complex entities as "compound actualities" rather than "compound substances." He explains that during the interaction of two entities, say entities A and B, when A acts on B, B reacts by receiving the effect from A and being internally affected by A, which influences the becoming of B and its character. In the same way, as B acts on A, A reacts and internalizes this action into its own becoming. This reciprocal transaction and influence of becoming sets up a bond between the two entities, by virtue of the reciprocal acting and reacting (Leclerc 1986, 166).

> By reason of the mutual actings and reactings, compound wholes are constituted which have a unity and thereby also a determinate character… Thus, from the combined acting and reacting of the constituents there emerges a new integral entity, a physical existent in the full sense of itself per se capable of acting. By such a compound entity's entering into interaction with other such entities, still more complex existents emerge. (Leclerc 1986, 167)

Leclerc explains that the being of a physical existent is constituted by its becoming. That is, the existence of an actuality is grounded in its becoming, and its character or definiteness, i.e., the 'what' it is, is the definiteness of its becoming.

4.4 Metaphysical Foundations for the Ontological Unity of bioS_{ipm}s

In the preceding sections, we reviewed a range of metaphysical positions that sought to account for the functional unity of actualities. At one extreme is Whitehead's position. Whitehead takes a reductionistic position, arguing that actualities are societies of actual entities, and thus

are only derivatively actual. At the other extreme are Aristotelian-Scholastic philosophers, who assert that the complex entities we encounter in nature, the horses, men, and molecules of our world, are actual, but their parts, say the atoms of a molecule, are present only virtually, and thus have no claim to authentic actuality. Contrary to both these positions are the metaphysical accounts of Neo-Whiteheadians and other philosophers who maintain, contra Whitehead, that the complex entities of nature are in fact ontologically actual, not derivatively so, and contra Aristotelian-Scholastic philosophers, are composed of entities that are themselves actual.

How does one assess the merits of these diverse metaphysical positions? How does one evaluate which best describes reality? My intent here is to let science be our guide, to "take scientific work as a starting point for metaphysical inquiry" (Chakravartty 2017, xiv).[16] First, when subjecting bioS_{ipm}s (i.e., metabolons) to metaphysical analysis, it is difficult to reconcile current biochemical findings with metaphysical positions that argue against the actuality of the enzymes that compose a metabolon, such Whitehead's philosophy of organism or Aristotelian-Scholastic substance philosophy. The findings of contemporary biochemistry establish that the enzymes of metabolons have a functional competency and structural integrity even when not complexed into metabolons. As James Felt (2001, 9) pointed out when discussing the parts of a whole, "the diversity of the required interrelated activities seems to require a certain independence for them even though they contribute to the whole." He goes on to ask a question that is key for us here: "Is it not possible to frame a theory of functional unity that accommodates a kind independence of its parts?"

As is clear from the preceding discussions, there are several metaphysical positions that can account for and ground the unity of the metabolon and at the same time allow for the actuality of the composing enzymes. From a non-Whiteheadian process perspective, Rescher would argue that metabolons are best described as "systemic wholes comprised of subordinate processes" (Rescher 1996, 55), where the enzymes of the metabolon and their individual catalytic activities are the "subordinate processes." And similarly, Dupré and Nicholson would maintain that the unity of a metabolon is "dynamically maintained by continuous activity taking place at higher and lower levels" (Dupré and Nicholson 2018, 27). Related to these processual positions, Leclerc would account for the global integration and functional unity of the metabolon by its existence as a compound actuality, where its ontological unity arises from reciprocally interacting component enzymes.

These metaphysical positions are similar in that they recognize the true actuality of the component enzymes of a metabolon, and account for its overall functional unity by the establishment and maintenance of intimate and dynamic relations among the composing enzymes. Importantly, these relations are entirely consistent with scientific investigations that have elucidated the physical forces (e.g., electrostatic forces and hydrogen bonding interactions) that stabilize and maintain the functional competence of metabolons.

Given the similarity of the positions of Rescher, Dupré, and Leclerc, development of a metaphysics to account for the unity of actualities that arise from intracellular pathways should draw inspiration from all three. Such a metaphysics will have two key features:

16. The possibility of using science as a metaphysical springboard to seek "the ontological implications of our best science" (Chakravartty 2017, xiv) reflects a commitment to a metaphysical stance variously known as naturalized metaphysics (Ladyman and Ross 2007), scientific ontology (Chakravartty 2017), scientific metaphysics (Ross, Ladyman, and Kincaid 2015), or the metaphysics of science (Mumford and Tugby 2013). The overarching premise of scientific metaphysics is that scientific findings can illuminate general structural features of the world and help us construct scientifically realistic ontologies. A corollary that guides the work of this paper is that well worked-out ontological systems have a role in helping us understand and interpret science at a level that is deeper than revealed by science itself.

- The ontological unity of a metabolon arises from relation – the complex interactions among the composing enzymes which maintain the structural integrity of the metabolon, set it apart from its environment, and account for its activity as pathway catalyst.
- The enzymes that compose the metabolon are themselves fully actual, and catalyze their individual reactions through internal relational processes that couple chemistry with protein dynamics (Alassia 2022; Guttinger 2018; 2021; Stein 2005; 2006; 2022).

5 Final Thoughts

How does an assembly of individual entities become a whole? What are the conditions under which this happens, if indeed it happens at all? Consider a gathering of four string musicians, say two violinists, a viola player, and a cellist, that have come together intent on playing a musical composition. Before the first strike of bow on string, they are simply four individual musicians; albeit related by a potentiality for unity. With the sounding of the first chord, this potentiality is realized – they are transformed into a functional whole. I submit that this transformation is ontological, resulting in an increase in ontological significance from a mere assembly of individuals into a musical performance unit.

These are the considerations we've been wrestling with in this paper, not in the domain of music, of course, but in the biochemical world. We've been asking if an assembly of functionally distinct enzymes can transform into something more, and in so doing acquire an ontological significance greater than the collection of these enzymes. I've argued that when an ensemble of enzymes that comprise an intracellular pathway are triggered into operation, this ensemble undergoes a transformation not only of function but also of ontological status – it becomes a functional whole, a biological system. Further, if these enzymes are organized in space as a structural assembly known as a metabolon, this functional whole acquires the ontological significance of an actuality, that is, an individuated physical entity that stands identifiably apart from its environment, and has an integrated internal complexity that allows it to interact with its environment and to operate as a unity within its environment.

We searched for possible metaphysical underpinnings of these transformations in three different metaphysical systems: process philosophy, Aristotelian-Scholastic substance philosophy, and Ivor Leclerc's philosophy of nature. These systems all regard nature as inherently dynamic and relational, and it is these features of reality that ultimately allow us to explain the unity of biological systems. We concluded that metabolons are best described within the context of a process metaphysics rather than a substance metaphysics and that the unity of metabolons arises from the complex relations among the composing, coupled enzymes, which are themselves fully actual.

Literature cited

Alassia, F. 2022. "A Process Ontolology Approach in Biochemistry: The Case of GPCRs and BioSignaling." *Foundations of Chemistry* 24: 405–22.

Allen, Doug K, and Jamey D Young. 2020. "Tracing Metabolic Flux through Time and Space with Isotope Labeling Experiments." *Current Opinion in Biotechnology* 64: 92–100. https://doi.org/10.1016/j.copbio.2019.11.003.

Araiza-Olivera, Daniela, Natalia Chiquete-Felix, Mónica Rosas-Lemus, José G. Sampedro, Antonio Peña, Adela Mujica, and Salvador Uribe-Carvajal. 2013. "A Glycolytic Metabolon in *Saccharomyces cerevisiae* Is Stabilized by F-Actin." *The FEBS Journal* 280 (16): 3887–905. https:

//doi.org/10.1111/febs.12387.

Armstrong, D. M. 2004. *Truth and Truthmakers*. Cambridge: Cambridge University Press. https://doi.org/10.1017/CBO9780511487552.

Austin, Christopher J. 2016. "The Ontology of Organisms: Mechanistic Modules or Patterned Processes?" *Biology and Philosophy* 31 (5): 639–62. https://doi.org/10.1007/s10539-016-9533-3.

Austin, Christopher J. 2017. "A Biologically Informed Hylomorphism." In *Neo-Aristotelian Perspectives on Contemporary Science*, edited by William M. R. Simpson, Robert C. Koons, and Nicholas J. Teh, 185–209. New York: Routledge.

Austin, Christopher J. 2020. "Organisms, Activity, and Being: On the Substance of Process Ontology." *European Journal for Philosophy of Science* 10 (2): 13. https://doi.org/10.1007/s13194-020-0278-0.

Austin, Christopher J., and Anna Marmodoro. 2017. "Structural Powers and the Homeodynamic Unity of Organisms." In *Neo-Aristotelian Perspectives on Contemporary Science*, edited by William M. R. Simpson, Robert C. Koons, and Nicholas J. Teh, 169–83. New York: Routledge.

Chakravartty, Anjan. 2017. *Scientific Ontology: Integrating Naturalized Metaphysics and Voluntarist Epistemology*. Oxford: Oxford University Press.

Clarke, W. Norris. 1993. "To Be Is To Be Substance-In-Relation." In *Metaphysics as Foundation: Essays in Honor of Ivor Leclerc*, edited by Paul A. Bogaard, Gordon Treash, and Ivor Leclerc, 164–83. Albany: SUNY Press.

Clarke, W. Norris. 2001. *The One and the Many: A Contemporary Thomistic Metaphysics*. Notre Dame, Indiana: University of Notre Dame Press.

Cobb, John B. 1965. *A Christian Natural Theology, Based on the Thought of Alfred North Whitehead*. Philadelphia: Westminster Press.

Cobb, John B. 1984. "Overcoming Reductionism." In *Existence and Actuality: Conversations with Charles Hartshorne*, edited by John B. Cobb, Jr., and Franklin I. Gamwell, 149–66. Chicago: University of Chicago Press.

Cohen, Rachel D., and Gary J. Pielak. 2017. "A Cell Is More than the Sum of Its (Dilute) Parts: A Brief History of Quinary Structure." *Protein Science* 26 (3): 403–13. https://doi.org/10.1002/pro.3092.

Dahmani, Ismail, Kezhen Qin, Youjun Zhang, and Alisdair R. Fernie. 2023. "The Formation and Function of Plant Metabolons." *The Plant Journal* 114 (5): 1080–92. https://doi.org/10.1111/tpj.16179.

Delafield-Butt, Jonathan. 2007. "Towards a Process Ontology of Organism: Explaining Behaviour in a Cell." In *Applied Process Thought I*, edited by Thomas Kelly and Mark Dibben, 237–60. Frankfurt: De Gruyter.

Dupré, John. 2015. "A Process Ontology for Biology." *Physiology News* (100): 33–34.

Dupré, John. 2020. "Life as Process." *Epistemology & Philosophy of Science* 57 (2): 96–113. https://doi.org/10.5840/eps202057224.

Dupré, John. 2021. "Processes within Processes: A Dynamic Account of Living Beings and Its Implications for Understanding the Human Individual." In *Biological Identity: Perspectives from Metaphysics and the Philosophy of Biology*, edited by Anne Sophie Meincke and John Dupré, 149–66. London: Routledge.

Dupré, John, and Daniel J. Nicholson. 2018. "A Manifesto for a Processual Philosophy of Biology." In *Everything Flows: Towards a Processual Philosophy of Biology*, edited by Daniel J. Nicholson and John Dupré, 3–46. Oxford: Oxford University Press.

Earley, Joseph E. 1981. "On Applying Whitehead's First Category of Existence." *Process Studies* 11 (1):

35–39. https://doi.org/10.5840/process19811113.

Earley, Joseph E. 2008. "Ontologically Significant Aggregation: Process Structural Realism (PSR)." In *Handbook of Whiteheadian Process Thought*, edited by Michel Weber and Will Desmond, 2–179. Frankfurt: De Gruyter.

Eslick, L. J. 1958. "Substance, Change, and Causality in Whitehead." *Philosophy and Phenomenological Research* 18: 503–13.

Estrada, Ernesto. 2023. "What Is a Complex System, After All?" *Foundations of Science*. https://doi.org/10.1007/s10699-023-09917-w.

Fani, Renato. 2012. "The Origin and Evolution of Metabolic Pathways: Why and How Did Primordial Cells Construct Metabolic Routes?" *Evolution: Education and Outreach* 5 (3): 367–81. https://doi.org/10.1007/s12052-012-0439-5.

Felt, James W. 2001. *Coming to Be: Toward a Thomistic-Whiteheadian Metaphysics of Becoming*. Albany: SUNY Press.

Feser, Edward. 2019. *Aristotle's Revenge: The Metaphysical Foundations of Physical and Biological Science*. Neunkirchen-Seelscheid: Editiones Scholasticae.

Glennan, Stuart. 2024. "The Mechanisms of Emergence." In *New Mechanism Explanation, Emergence and Reduction*, edited by João L. Cordovil, Gil Santos, and Davide Vecchi, 213–34. Cham: Springer.

Griffin, David R. 1988. "Of Minds and Molecules: Postmodern Medicine in a Psychosomatic Universe." In *The Reenchantment of Science: Postmodern Proposals*, edited by David R. Griffin, 141–64. Albany, SUNY Press.

Griffin, David Ray. 1997. "Panexperiential Physicalism and the Mind-Body Problem." *Journal of Consciousness Studies* 4 (3): 248–68.

Guttinger, Stephan. 2018. "A Process Ontology for Macromolecular Biology." In *Everything Flows: Towards a Processual Philosophy of Biology*, edited by Daniel J. Nicholson and John Dupré, 303–20. Oxford: Oxford University Press.

Guttinger, Stephan. 2021. "Process and Practice: Understanding the Nature of Molecules." *HYLE - International Journal for Philosophy of Chemistry* 27: 47–66.

Harris, Errol E. 1965. *The Foundations of Metaphysics in Science*. London: George Allen & Unwin Ltd.

Harris, Errol E. 1970. *Hypothesis and Perception. The Roots of Scientific Method*. London: George Allen & Unwin Ltd.

Hartshorne, C. 1936. "The Compound Individual." In *Philosophical Essays for Alfred North Whitehead*, edited by Otis H. Lee, 193–220. New York: Longmans Green.

Jaeger, Johannes, and Nick Monk. 2015. "Everything Flows: A Process Perspective on Life." *EMBO Reports* 16 (9): 1064–67. https://doi.org/10.15252/embr.201541088.

Kaiser, Marie I. 2013. "Complexity." In *Encyclopedia of Systems Biology*, edited by Werner Dubitzky, Olaf Wolkenhauer, Kwang-Hyun Cho, and Hiroki Yokota, 456–60. New York: Springer.

Kastritis, Panagiotis L., and Anne-Claude Gavin. 2018. "Enzymatic Complexes across Scales." *Essays in Biochemistry* 62 (4): 501–14. https://doi.org/10.1042/EBC20180008.

Kondrat, Svyatoslav, and Eric von Lieres. 2022. "Mechanisms and Effects of Substrate Channelling in Enzymatic Cascades." *Methods in Molecular Biology* 2487: 27–50. https://doi.org/10.1007/978-1-0716-2269-8_3.

Kopel, Jonathan. 2019. "A Note Regarding Relational Ontology in Chemistry." *Process Studies* 48 (1): 59–66. https://doi.org/10.5840/process20194815.

Ladyman, James, James Lambert, and Karoline Wiesner. 2013. "What Is a Complex System?" *European Journal for Philosophy of Science* 3 (1): 33–67. https://doi.org/10.1007/s13194-012-0056-8.

Ladyman, James, Don Ross, David Spurrett, and John Collier. 2007. *Every Thing Must Go: Metaphysics Naturalized*. Oxford: Oxford University Press.

Laszlo, Ervin. 1972. *Introduction to Systems Philosophy. Toward a New Paradigm of Contemporary Thought*. New York: Harper & Row Publishers.

Leclerc, Ivor. 1972. *The Nature of Physical Existence*. London: George Allen & Unwin Ltd.

Leclerc, Ivor. 1986. *The Philosophy of Nature*. Washington, D.C.: Catholic University of America Press.

Lyubarev, A. E., and B. I. Kurganov. 1989. "Supramolecular Organization of Tricarboxylic Acid Cycle Enzymes." *Bio Systems* 22 (2): 91–102. https://doi.org/10.1016/0303-2647(89)90038-5.

Meincke, Anne Sophie. 2018. "Persons as Biological Processes: A Bio-Processual Way Out of the Personal Identity Dilemma." In *Everything Flows: Towards a Processual Philosophy of Biology*, edited by Daniel J. Nicholson, and John Dupré, 357–78. Oxford: Oxford University Press.

Meincke, Anne Sophie. 2019. "Human Persons – A Process View." In *Was sind und wie existieren Personen? Probleme und Perspektiven der gegenwärtigen Forschung*, edited by Jörg Noller, 53–76. Mentis: Brill.

Meincke, Anne Sophie. 2021. "Bergson and Process Philosophy of Biology." In *The Bergsonian Mind*, edited by Mark Sinclair, and Yaron Wolf, 432–45. Routledge.

Morgan, William. 2021. "Are Organisms Substances or Processes?" *Australasian Journal of Philosophy* 100 (3): 605–19. https://doi.org/10.1080/00048402.2021.1931378.

Mumford, Stephen, and Matthew Tugby. 2013. "What is the Metaphysics of Science?" In *Metaphysics and Science*, edited by Stephen Mumford and Matthew Tugby, 3–28. Oxford: Oxford University Press.

Nicholson, Daniel J. 2018. "Reconceptualizing the Organism: From Complex Machine to Flowing Stream." In *Everything Flows: Towards a Processual Philosophy of Biology*, edited by Daniel J. Nicholson, and John Dupré, 139–66. Oxford: Oxford University Press.

Nicholson, Daniel J. 2019. "Is the Cell Really a Machine?" *Journal of Theoretical Biology* 477: 108–26. https://doi.org/10.1016/j.jtbi.2019.06.002.

Nicholson, Daniel J., and John Dupré. 2018. *Everything Flows: Towards a Processual Philosophy of Biology*. Oxford: Oxford University Press.

Novikoff, Alex B. 1945. "The Concept of Integrative Levels and Biology." *Science* 101 (2618): 209–15. https://doi.org/10.1126/science.101.2618.209.

Oderberg, David S. 2007. *Real Essentialism*. New York: Routledge.

Oderberg, David S. 2017. "The Great Unifier: Form and the Unity of the Organism." In *Neo-Aristotelian Perspectives on Contemporary Science*, edited by William M. R. Simpson, Robert C. Koons, and Nicholas J. Teh, 211–33. New York: Routledge.

Pedley, Anthony M., Vidhi Pareek, and Stephen J. Benkovic. 2022. "The Purinosome: A Case Study for a Mammalian Metabolon." *Annual Review of Biochemistry* 91:89–106. https://doi.org/10.1146/annurev-biochem-032620-105728.

Rescher, Nicholas. 1996. *Process Metaphysics: An Introduction to Process Philosophy*. Albany: SUNY Press.

Ross, Don, James Ladyman, and Harold Kincaid, eds. 2015. *Scientific Metaphysics*. Oxford: Oxford University Press.

Sfekas, Stanley. 1991. "Ousia, Substratum, and Matter." *Philosophical Inquiry* 13: 38–47. https://doi.org/10.5840/philinquiry1991131/23.

Skalidis, Ioannis, Christian Tüting, and Panagiotis L. Kastritis. 2020. "Unstructured Regions of Large Enzymatic Complexes Control the Availability of Metabolites with Signaling Functions." *Cell Communication and Signaling* 18 (1): 136. https://doi.org/10.1186/s12964-020-00631-9.

Srere, Paul A. 1985. "The Metabolon." *Trends in Biochemical Sciences* 10 (3): 109–10. https://doi.org/10.1016/0968-0004(85)90266-X.

Stein, Ross L. 2004. "Towards a Process Philosophy of Chemistry." *HYLE - International Journal for Philosophy of Chemistry* 10: 5–22.

Stein, Ross L. 2005. "Enzymes as Ecosystems: A Panexperientialist Account of Biocatalytic Chemical Transformation." *Process Studies* 34 (1): 62–80. https://doi.org/10.2307/44797644.

Stein, Ross L. 2006. "A Process Theory of Enzyme Catalytic Power – The Interplay of Science and Metaphysics." *Foundations of Chemistry* 8 (1): 3–29. https://doi.org/10.1007/s10698-005-7907-8.

Stein, Ross L. 2008. "On Molecules and Their Chemical Transformation." In *Handbook of Whiteheadian Process Thought*, edited by Michel Weber, 171–78. Frankfurt: De Gruyter.

Stein, Ross L. 2011. *Kinetics of Enzyme Action: Essential Principles for Drug Hunters*. Hoboken, NJ: Wiley.

Stein, Ross L. 2022. "Mechanisms of Macromolecular Reactions." *History and Philosophy of the Life Sciences* 44 (2): 11. https://doi.org/10.1007/s40656-022-00492-0.

Steward, Helen. 2020. "Substances, Agents and Processes." *Philosophy* 95 (1): 41–61. https://doi.org/10.1017/s0031819119000494.

Berg, Jeremy M., John L. Tymoczko, and Lubert Styer. 2019. "16.2 The Glycolytic Pathway Is Tightly Controlled." In *Biochemistry*. W.H. Freeman & Co Ltd.

Sweetlove, Lee J., and Alisdair R. Fernie. 2018. "The Role of Dynamic Enzyme Assemblies and Substrate Channelling in Metabolic Regulation." *Nature Communications* 9 (1): 2136. https://doi.org/10.1038/s41467-018-04543-8.

Tian, Tian, Jun Fan, and Shannon Elisabeth Elf. 2021. "Metabolon: A Novel Cellular Structure That Regulates Specific Metabolic Pathways." *Cancer Communications* 41 (6): 439–41. https://doi.org/10.1002/cac2.12154.

Wallack, F. Bradford. 1980. *The Epochal Nature of Process in Whitehead's Metaphysics*. Albany: SUNY Press.

Whitehead, Alfred N. [1925] 1967. *Science and the Modern World*. New York: MacMillan Publishing Company.

Whitehead, Alfred N. [1929] 1978. *Process and Reality*. New York: MacMillan Publishing Company.

Whitehead, Alfred N. [1933] 1967. *Adventures of Ideas*. New York: The Free Press.

Wimsatt, William C. 2007. *Re-Engineering Philosophy for Limited Beings: Piecewise Approximations to Reality*. Cambridge, MA: Harvard University Press.

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