The Ontology of Physics for Biology — a companion to Basic Formal Ontology

Daniel L. Cook[a,b], John H. Gennari[a], Maxwell L. Neal[c]

[a] *Department of Biomedical Informatics and Medical Education, University of Washington, Seattle, Washington, USA*
[b] *Department of Physiology and Biophysics, University of Washington, Seattle, Washington, USA*
[c] *Center for Global Infectious Disease Research, Seattle Children's Research Institute, Seattle, Washington, USA*

Abstract

The Ontology of Physics for Biology (OPB) has been developed to annotate and reason over the physical and system dynamical content of physiological simulation models and data sets. It has been built in the context of Open Biomedical Ontology (OBO) upon which we rely for annotating the biological content of biological simulation and analysis models. However, there is little ontological support for basic concepts, entities, and laws of classical physics that are the bases of our physics-based understanding of how and why biophysical processes occur as they do. To address this gap, we developed the Ontology of Physics for Biology as a formal representation of energy-bearing biophysical entities, their observable physical properties, and the quantitative dependencies (i.e., laws) amongst the values of those properties. In this paper, we review the OPB's representation of system dynamics and introduce extensions for representing entities, properties, and dependencies of thermodynamics. Based on these representations, we propose a thermodynamics-based definition of dynamical biological process as the flow of thermodynamical energy. It is yet to be determined how these essential aspects of classical physics lie within or relate to the ontological framework of the Basic Formal Ontology (BFO). We suggest that the OPB can function as a companion ontology to BFO in the domain of system dynamics and thermodynamics.

Keywords:

physics ontology, bioengineering, system dynamics, thermodynamics, biophysical modeling

Biophysical modeling and ontologies

Physics-based mathematical modeling and analysis of biological processes can provide insight into understanding physiology and pathophysiology. Early models (1,2) in the mid-20th century laid the foundations for our understanding of the biophysics of enzymatic reactions, neuronal ion channel gating, and the integrated behavior of complex metabolic networks. Since these seminal studies, physics-based computational modeling has expanded for all biophysical domains and disciplines and across all spatiotemporal scales.

These models have been critical resources for a series of multiscale physiological modeling projects such as DARPA's Virtual Soldier Project (VSP, http://www.virtualsoldier.us/), the EU's Virtual Physiological Human project (VPH; https://www.vph-institute.org/), the NIH's Virtual Physiological Rat project (VPR; http://virtualrat.org/), and the Center for Reproducible Biomedical Modeling (https://reproduciblebiomodels.org/). Each of these projects was a multicenter collaboration of mathematical modelers of physics-based physiological and pathophysiological systems across temporal and spatial scales. Each project addressed major challenges in finding, accessing, and reusing the contents of available model repositories and biomedical database resources.

The results and knowledge from these projects comprise what physiological modelers have dubbed the "physiome" (3,4). The multiscale, multidomain physiome has been the focus of ambitious projects such as the EBI-sponsored VPH project (5). The results of these and other efforts are a number of model repositories such as BioModels (EBI; https://www.ebi.ac.uk/biomodels/) and the Physiome Model Repository (https://models.physiomeproject.org/welcome).

These projects have faced major challenges of data access and alignment and the more general problems of computer model interoperability and reproducibility. Serious syntactic problems stemmed from using different modeling languages and computational platforms despite the availability of web-friendly languages (e.g. the Web Ontology Language, OWL) and data exchange standards. Such problems were, and are, symptomatic of pervasive and intractable semantic problems that are the product of so-called "silo" thinking, use of local jargons, and domain-specific terminologies.

In response, the biomedical community advocated the use of semantically rich ontologies, as available in growing collections such as the Open Biomedical Ontology collection (OBO; http://www.obofoundry.org/) and BioPortal (https://bioportal.bioontology.org/). Interoperability of these ontologies has been greatly enhanced by the strong unifying spatio-temporal, "realist" framework provided by the Basic Formal Ontology (BFO) (6).

However, the BFO framework only partially meets the needs of biophysical investigators and modelers as it offers scant representation of those physical properties, biophysical laws, and thermodynamic constraints that are the foundations of biophysical analysis, modeling, and data representation. Whereas BFO and OBO ontologies are based on the philosophical perspective of "realism", the Ontology of Physics for Biology (OPB) (7,8) is based on biophysical theory and bioengineering practices as used by generations of physical scientists for concise and predictive means for representing, analyzing, and explaining biophysical entities and processes.

In this paper, we describe the OPB representational schema focusing on four aspects of biophysics: 1) We define OPB dynamical property classes based on "stock-and-flow" system dynamic modeling; 2) we describe "physical dependency" classes that represent physical laws such as Ohm's Law that apply across multiple biodynamical domains; 3) we describe OPB representation of thermodynamical energy and entropy; and 4) we propose to define and classify biophysical processes as the flow of energy and/or information. We focus on these four aspects of the OPB that may present challenges to integrating and interoperating with BFO realism-based ontologies.

Challenges of representing biophysics

Our representational challenge has been to define and represent the physical attributes and the physical laws that are the basis for biophysical analysis and modeling. Physical properties such as flow rate, pressure, and flow resistance must be defined in a manner that is useful for applying basic *constitutive* laws such as Hooke's law or Ohm's law. *Constraints*, such as for conservation of mass and charge, must govern the values of such properties. Such laws and constraints are expressed as mathematical abstractions that include differential and integral calculus.

Available ontology resources

Annotating computational, biophysical models benefits greatly from access to existing repositories of structural knowledge—ontologies—that span all spatial scales for annotating structural participants in computational models. In particular, there exists a wide range of ontologies of biological structures and processes that are now available on the web, such as those hosted at the European Bioinformatics Institute (https://www.ebi.ac.uk/ols/ontologies). The following list exemplifies the span of structural and temporal scales represented in selected OBO ontologies:

- Foundational Model of Anatomy (FMA): organ systems, organs, tissues, cells
- Cell Ontology (CO): cells and cell parts
- Gene Ontology (GO): genomic components
- GO-Plus: processes and participants
- Protein Ontology (PO): proteins
- ChEBI: small molecules, ions

To frame the content of these ontologies, the BFO offers two key classes: BFO:*continuant* represents discrete, space-occupying, temporally-persistent material things that are the participants in BFO:*process* (subclass of BFO:*occurrent*) that represents what happens to continuants that are participating in the process for an interval of time. The OBO repository ensures conformance with the Basic Formal Ontology (BFO) and with the Relations Ontology (RO) that represents and defines spatial relations.

Need for an ontology of biophysics

A major challenge to quantitative biophysical modeling by bioengineers is that, although they may adhere to a common understanding of physics, they employ a variety of space-time coordinate systems, mathematical formalisms, languages, data structures, and computational platforms to encode and compute model prediction and insights. The resulting "tower of Babel" is a major impediment to knowledge sharing and hinders collaborative work. We were thus motivated to develop an ontology of classical physics to mediate the representation and exchange of biophysical knowledge across physical, mathematical, and physiological domain boundaries.

Although there are excellent resources for these structural elements, we find that there are scant resources for the representation of biophysical laws (e.g. Ohm's law) and the processes that they govern. Borst, et al. developed the PhysSys Ontology (9; no longer available) which foreshadowed key elements of the OPB but was restricted to the domain of engineering system dynamics. Gruber (10) developed an Ontology of Engineering Mathematics (no longer available) which focused on the mathematical abstractions without being tailored to biological systems analysis.

Our key representational goals for the OPB have been to: 1) provide explicit physics-based definitions and classification of observable physical properties such as mass, flow rate, and temperature, 2) represent physical processes according to the system dynamical architecture of stocks and flows, 3) represent the mathematics of infinite and infinitesimal spans of time and space, 4) extend the domain of continuants to include electrical charge and thermodynamic energy, and 5) define and classify the laws and axioms of physics for mapping onto the mathematics of analytical models.

OPB development, implementation, and use

In developing a formal ontology of biophysics and systems dynamics that could serve the large biophysical analysis and modeling communities, we recognized the value of following the representational guidelines of the BFO and OBO. This perspective was inspired by our colleagues at the University of Washington who developed and maintain the Foundational Model of Anatomy (FMA). Some aspects of OPB development have been reported {Cook, 2011 #522;Neal, 2013 #813;Neal, 2016 #1006}) and presented to prior meetings of the International Conference on Biomedical Ontology (ICBO).

The OPB has a growing impact in the biomodeling domain as evidenced by our participation in the Computational Modeling in Biology Network (COMBINE, https://co.mbine.org) to develop tools and standards that are responsive to that community's user base. Most recently, these collaborations have led to our participation in the Center for Reproducible Biomedical Modeling (http://reproduciblemodels.org/). As part of this center, and with collaborators at the Auckland Bioengineering Institute, we have recently established a pipeline with several peer-reviewed journals whereby models associated with new publications would be annotated and curated by staff in the Center prior to publication and dissemination by the journal. These annotations use the framework provided by the OPB as well as tools such as SemGen (12,13,14) and others that rely on the semantics of the OPB for representing the mathematical and biophysical properties of these models.

OBP domain content has been gleaned from physics and biophysics textbooks, literature resources, online resources, and extensive discussions with a broad range of biophysical and physiological modelers. We have sought to represent the biophysical entities, theories and computations used by physiologists, biophysicists, and bioengineers to represent and analyze physical entities and processes in biological systems. In doing so, the OPB adopts basic BFO spatiotemporal classes such as for *continuants* and *occurrents* but is expanded to represent immaterial aspects of biophysical reality such as energy, electrical charge, and physical laws.

We have strived to structure the OPB to map as well as possible to the BFO and OBO ontologies. However, as others have noted (15), there are key mathematical concepts such as temporal and spatial differentiation and integration of property values that are outside of the realist framework. Furthermore, key physical entities that are immaterial (thermodynamic energy and entropy), dynamical laws, and unbounded spatiotemporal entities (gravitational fields) do not fit comfortably into the realist representational framework.

Physiological modeling

Biophysicists, bioengineers, and physiologists aim to understand the structural, thermodynamic, and system dynamic basis of physiological function across structural and temporal scales. We are inspired by important questions such as: how do the parts of the cardiovascular system combine to finely regulate heart rate, cardiac contractility, and vascular resistance to maintain blood pressure? How do pancreatic beta-cells control insulin secretory rate to regulate blood glucose? Answers to such clinically and biologically important questions are described as physiological hypotheses, subjected to laboratory evaluation, and formalized as physics-based mathematical models based on the principles of classical physics.

Our goal has been to represent the biophysical aspects of continuants and processes across biophysical domains (electrophysiology, fluid dynamics, etc.) that span spatial scales from atomic to organismal. The OPB represents biophysical reality as it is perceived, measured, and analyzed by generations of clinicians, physiologists, and bioengineers. Accordingly, our measure of success is the degree to which we can annotate and reason over the explanatory constructs that constitute the broad range of biological system dynamical knowledge and analytical methods.

In the following, we describe key features of the OPB, focusing on those aspects that include abstract models of mathematics and biophysics. Recently, we have extended the OPB to include definitions of thermodynamic entities (energy, entropy, etc.) and representations of the laws by which they depend upon one another. We also describe extensions to the OPB that formalize the representation of spatiotemporal continua and of thermodynamics in support of recent advances in energy bond-graph modeling (16-18).

OPB overview

The OPB represents those aspects of the real world that can be and have been represented analytically using the theories, mathematics, and procedures of classical physics. It represents the quantitative aspects of biomedical reality by identifying physically observable attributes of physical continuants and processes, and offering classes that represent theorems, physical laws, and analytical procedures for explaining prior events and for predicting future events.

Physics is a quantitative, computational science based on defining and quantifying the observable properties of physical entities and then specifying quantitative rules and laws by which such quantities depend upon one another. Chemistry is the science responsible for identifying and quantifying atomic and molecular species and then discovering and specifying, for example, the quantitative reaction laws that specify chemical reaction rates. Hydraulics is the science of fluid quantities and fluid flows. Electricity is the

science of electrical charges and charge flow. Each of these physical sciences are concerned with the amounts of "stuff" (e.g., material, charge, momentum) and the rules that determine rates of flow or exchange during physical processes.

The upper three OPB class levels are shown in Figure 1. The top class OPB:*Physics entity* is defined as "A *Thing* that is a quality, definition, abstraction, or law of classical physics as discovered and applied to the explanation, analysis, and simulation of biophysical entities and processes." The next two subclasses distinguish classes that represent real from analytical entities as: 1) OPB:*Physics real entity* is defined as "A *physics entity* that is a continuant or process in the real world and that occupies space and time, and is composed of portions of matter, energy, or information." The second subclass, OPB:*Physics analytical entity* is defined as "A *physics entity* that encodes or expresses a theory, hypothesis, or explanation that relates instances of physics continuants and processes for purposes of demonstration, calculation, education, or simulation."
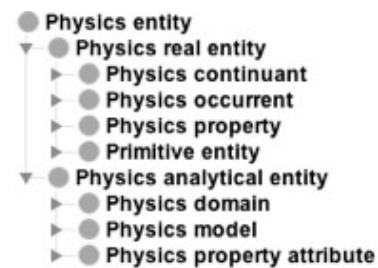

- ⬤ Physics entity
  - ▼ ⬤ Physics real entity
    - ▶ ⬤ Physics continuant
    - ▶ ⬤ Physics occurrent
    - ▶ ⬤ Physics property
    - ▶ ⬤ Primitive entity
  - ▼ ⬤ Physics analytical entity
    - ▶ ⬤ Physics domain
    - ▶ ⬤ Physics model
    - ▶ ⬤ Physics property attribute

Figure 1. OPB top classes in the Protégé ontology editor

The system dynamics perspective of the OPB

Whether explicitly or implicitly, biophysical modeling adopts a generalized "stock-and-flow" system dynamic modeling paradigm based on *stocks* of "stuff" (i.e., *continuants*) coupled by *flows* of "stuff" (i.e., *processes*) amongst the stocks. Bank accounts work that way. Inventories work that way. Automobile gas tanks and batteries work that way. Biophysical systems work that way. The key modeling tasks are to: 1) define *amounts* of stuff in each stock, 2) define *flow rates* of stuff amongst stocks, 3) apply *conservation constraints* by which *amounts* depend on *flow rates*, 4) apply *constitutive laws* by which *flow rates* depend on *amounts*.

A key feature of computational system dynamics is that it is concerned solely with the *values* of the physical properties (e.g., amounts of material, velocity of motion) of the modeled continuants and occurrents. The continuants (e.g., heart, blood, cell) and processes (beating, flowing, migrating) are implicit in the mathematics and their identities are established only by annotations against appropriate ontologies such as in the OBO collection. Furthermore, some models may simply represent generalized, hypothetical abstractions pertinent to broad classes of continuants and processes.

OPB:Physical properties

Physical properties are the physically observable attributes (phenotypes) of physical participants of physical processes across all spatiotemporal scales and across all biophysical domains (see Figure 2). We have defined (7) the OPB:*Physical property* class as "A physics real entity that is a physically observable attribute

of a physics continuant or process that can be represented as a scalar, vector or tensor, or as an aggregate of such measures, or as can be computationally derived from such measures." Key subclasses are shown in Figure 2.

Figure 2. OPB:Dynamical property classes represent the physically observable properties of continuants and occurrents and of the constitutive relations amongst such properties.

Dynamical property classes constitute a dual-inheritance hierarchy whereby each property is a subclass of OPB:*Dynamical property* and of OPB:*Dynamical domain* (Figure 3).
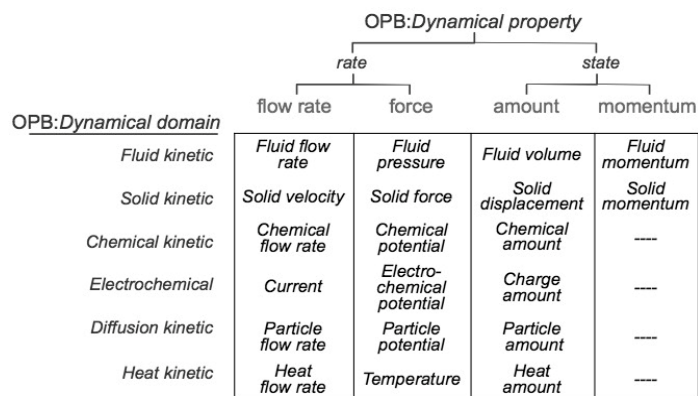
Figure 3. OPB:Dynamical property classes comprise a dual-inheritance hierarchy of four OPB:Dynamical property subclasses and six OPB:Dynamical domain subclasses.

The OPB:*Dynamical property* class distinguishes two subclasses OPB:*Dynamical rate property* and OPB:*Dynamical state property* that apply to each of six OPB:*Dynamical domains* as shown in Figure 3. For example, blood flowing across the boundary of a vessel would have an instance of OPB:*Fluid flow rate* as a physical property. Its quantitative value may be expressed in various units (gal/hr, l/min, etc.) and may represent bulk flow rate fluid though an entire conduit, or a vector flow rate at a point in a flow field. The corresponding state property for the portion of fluid in the vessel (OPB:*Portion of fluid*) is an instance of OPB:*Amount of fluid* and would quantify the amount of a portion of fluid in, say, pints or milliliters, or as fluid density (OPB:*Volume density of material*).

These properties are defined according to the stock-and-flow kinetics as reciprocal relations whereby the *amount* of a stock is equal to the *temporal integral* of the net *flow rate* of stuff into the stock, and the net *flow rate* from the stock is the temporal derivative of the *amount* in the stock:

$$\text{amount} = \int (\text{flow rate}) \, dt$$

$$\text{flow rate} = d/dt \, (\text{amount})$$

The OPB represents subclasses of OPB:*Amount property* and of OPB:*Flow rate property* for each of the six OPB:*Dynamical domains* (Figure 3) as a dual inheritance hierarchy (7) based on property kind (OPB:*Dynamical property*) and domain (OPB:*Dynamical domain*). A less familiar but nonetheless important, temporal relationship between is the one between subclasses representing momentum (OPB:*Dynamical momentum property*) and representing force (OPB:*Dynamical force property*) that applies to material continuants analogously to that of amount and flow rate. Hence, momentum = ∫ (force) dt, and force = d/dt (momentum). These quantitative dependencies are fundamental property value constraints of dynamical modeling according to physical "laws".
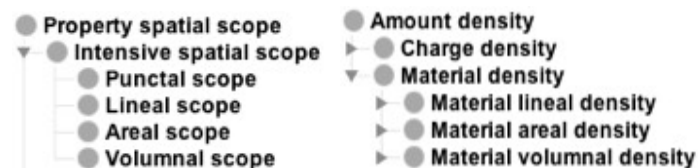

Figure 4. OPB:Property spatial scope classes (on left) are juxtaposed against OPB:Amount density subclasses (right panel) for a given spatial scope.

Figure 4 illustrates a representational choice that we have yet to resolve as a "best practice". In the left hand panel, we show OPB:*Material density* subclasses of OPB:*Physical property* which include subclasses that scale material mass across lineal, areal, and volumnal spatial spans. This representational strategy "precoordinates" material amounts with spatial spans to represent material spatial densities. The alternative representational strategy is to annotate density properties by "postcoordinating" a OPB:*Material amount* instance with an OPB:*Property spatial scope* instance. The curatorial advantage of the latter strategy is that it obviates explicitly representing every class that combines property kind and a spatial scope. For annotating biophysical data and model variables we adopted a post-coordination strategy to solve the combinatoric explosion of attributing to every physical entity class (e.g., FMA classes) each physical property class that may apply. It remains to be determined whether pre- or post-coordination best suits the representation of physical properties variants in Figure 5.

In effect, we have adopted a *post-coordination* strategy for annotating data and variables, as needed, to declare their particular attributes. Otherwise, the OPB would be burdened to *a priori* represent all possible property instances rather than relying on applications to annotate and interpret property attributes as are relevant to a particular application. We welcome further discussion with BFO community members to determine whether this approach harmonizes with the representational logic underlying BFO:*Quality* and its subclasses.

Property expression variants

All dynamical properties—masses, forces, flow rates, volumes, etc.—exist and are quantifiable at every temporal instant for every instance of a physical continuant or occurrence. In that sense, such attributes are as real as the continuant or process property that bears the value. A common problem is that an observed property instance may be modeled differently by different modelers. For example, different models could regard the same observed

force as a 3-dimensional vector quantity, as a scalar quantity, or as a 2-dimensional array of surface-normal mechanical stresses. Each representation readily transforms into the others, but they must be distinguished by annotations.

However, representing the specific physical meaning of a physical property can be documented using subclasses of the OPB:*Physics property variant* class (Figure 5).
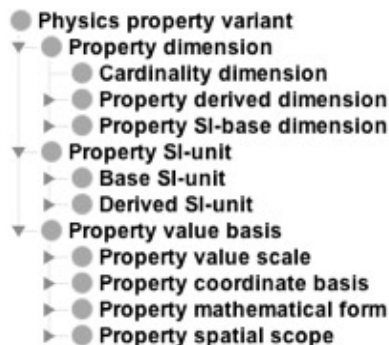

Figure 5. OPB:Physics property variant subclasses for annotating physical property instances.

OPB:Dynamical dependencies

Dynamical dependencies define and distinguish state and rate properties across dynamical domains and do so in a widely recognized network of properties and their dependencies (9, 17, 20). The OPB network version is shown in Figure 6 where physical property instances are represented as ovals and their physical dependencies as arcs bearing rectangles. Dynamical dependencies representing calculus functions (squares on left side of Figure 6) are labeled "d/dt" for temporal derivatives (OPB:*Temporal derivative constraint*) or "∫dt" for temporal integrals (OPB:*Temporal integral constraint*).
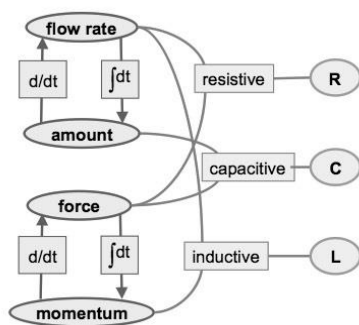

Figure 6. System dynamical framework is a self-referential network by which the values of OPB:Physical property instances (ovals) depend upon one another according to instances of OPB:Dynamical dependencies (rectangles) that represent biophysical laws and equations. OPB:hasPropertyPlayer relations (lines) link dependencies to their property players. "R" = resistance, "C" = capacitance, "L" = inductance.

We first describe OPB:*Constraint dependency* classes that represent the conservation laws for matter, energy, and momentum. We then turn to representing the more pleomorphic law represented as OPB:*Constitutive dependency* classes

OPB:Constraint dependency

OPB:*Constraint dependency* classes (see Figure 7) represent conservation constraints as defined by the fundamental theorems of calculus. For example, the net change in the value of a conserved quantity within a spatial boundary, over a span of time, is a temporal integral of the flow rate across that boundary. Thus, OPB:*Constraint dependency* instances are purely mathematical constraints on the value of a conserved quantity such as for a volume change due to a fluid flow, a change in electrical charge due to an electrical current, or the movement of an object for a certain distance.
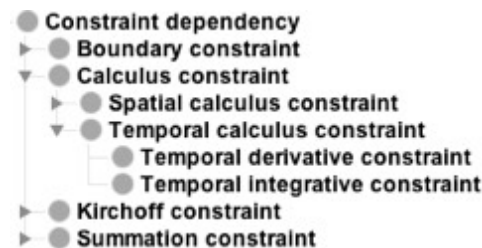

Figure 7. Key subclasses of OPB:Constraint dependency

The OPB expresses these essential relations as flows (OPB:*Dynamical flow rate*) and amounts (OPB:*Dynamical amount*) as shown as ovals in Figure 6. The essential mathematics of these relationships are that the temporal integral ("∫dt") of a *rate* property value determines the resulting change in a corresponding *state* property value (or, reciprocally, the temporal differential ("d/dt") of a *state* property value to determine a *rate* property).

For example, the increment of fluid volume due to fluid inflow is the flow rate times the interval of flow if the flow rate is constant. If not constant, the change in volume is the (definite) temporal integral of the flow rate as a function of time over the time interval: $\Delta V = \int F(t)\,dt$. Or, by the mathematical inverse, the rate of change of volume equals the fluid flow rate; $dV/dt = F(t)$. By analogy to the relationship of *flow rates* to *amounts*, there is a corresponding, but less familiar dynamical relationship between *forces* and *momenta* as diagrammed in the lower part of Figure 4. Such analogies define *state* and *rate* dynamical properties across all physical domains. These property/dependency relations are mapped diagrammatically on the left side of Figure 4 as integrals and derivatives.

These figures represent all such domain-independent "stock and flow" relationships between flow rates of stuff (OPB:*Dynamical flow rate*) and the changes in the amount of stuff (OPB:*Dynamical amount*). Some dependencies represent the accumulation and depletion of stocks (e.g., material, charge, momentum) due to inflows and outflows. These are represented by subclasses of OPB:*Temporal calculus constraint*. OPB:*Temporal constraint* (i.e., dx/dt) represents how the rate of change of the amount of a stock equals the flow rate across the boundary of the stock. And, inversely, OPB:*Temporal integral* (i.e., ∫xdt) represents how much a the amount of a stock changes during a period of time given the flow rate across its boundary. The OPB:*Temporal calculus constraint* (Figure 5) also holds that any material object (i.e., composed of matter) to which solid force or fluid pressure is applied possesses momentum in proportion to its mass, m, and velocity, v, such that their product, mv, is its momentum (OPB:*Translational momentum*). Figure 4 shows that

such dependencies apply to the physical relationship between forces and the momentum of a material object to which the force is applied.

These are examples of the fundamental importance of temporal and spatial continua, and their continuous derivatives and integrals to our understanding, representation, and analysis of biodynamical systems. Yet, as we understand it, such temporal and spatial derivatives and integrals have no representational support in BFO (15).

> **Issue 1:** *How to represent spatial and temporal derivatives of the quantitative values of physical properties?*

OPB:Constitutive dependency

As opposed to OPB:*Constraint dependency* classes, OPB:*Constitutive dependency* classes represent "constitutive laws" that are known only by empirical observations and descriptions. They may be simple linear relations as first described by mid-nineteenth century scientists who identified the three fundamental relations shown as arcs with rectangles in Figure 4. Such constitutive laws may be characterized by linear coefficients such as resistance (R) for Ohm's law, capacitance (C) for Faraday's law, and inductance (I) for Henry's law. These linear coefficients are represented as subclasses of OPB:*Constitutive proportionality* such as OPB:*Fluid flow resistance.* However, biophysical phenomena and models are rife with non-proportional (i.e., nonlinear) constitutive dependencies such as for the Michaelis-Menten enzyme kinetic model for which OPB includes classes such as OPB:*Property of non-proportional chemical rate law* that includes subclasses for "Km" and "Vmax", the Michaelis-Menten model parameters.

Dependency network defines dynamical properties circularly

The closed topology of the dependency network diagrammed in Figure 4 has profound ontological implications for the understanding of systems dynamics properties: 1) masses, flows, flow resistances, etc. are defined in a manner that is entirely circular, thus 2) no single property has primacy for defining and evaluation other properties. Consequently, the calibration of physical measurement devices depends on established standards such as those of the Systeme Internationale (SI).

Thermodynamical entities and dependencies

Thermodynamics represents principles and constraints on whether and how fast all biological processes occur. Yet the most foundational thermodynamical quantity, energy, receives only scant representation in available ontologies such as the BFO, GFO, and other OBO ontologies. However, thermodynamics principles are fundamental to all manner of biophysical processes and physics-based analyses performed by bioengineers, biophysicists, and physical biochemists.

Thermodynamics is a facet of reality as expressed by its two key thermodynamic quantities—*energy* and *entropy*—that are defined and known solely by computations on observable physical properties. Beyond such computations there are no other definitions of these terms. As expressed by Nobel Prize-winning physicist Richard Feynman (19):

"What we have <u>discovered</u> about energy is that we have a scheme with a set of <u>rules</u>. From each set of rules we can calculate a number for each kind of energy. When we add all the numbers together, from all the different kinds of energy, we always get the same total. But as far as we know there are no real units, no little ball bearings. It is abstract, purely mathematical that there is a number such that when you calculate it, it does not change. I cannot interpret it better than that."

— Richard Feynman

Thus, energy, like other physical entities and properties, is an entity with properties that exist and are discovered and defined as entities and dependencies of classical physics. Despite their ineffable natures, thermodynamic entities and their quantification are inferred from values of dynamical properties according to the values of observable amount and flow rates. Figures 8 and 9 show some of these relationships, and some key definitions of thermodynamical entities are as follows:

- OPB:*Portion of kinetic energy* — A *portion of energy* proportional to velocity or rate of flow of a material or electrical charge.

- OPB:*Portion of potential energy* — A *portion of energy* proportional to the amount and displacement of a dynamical entity in a potential energy field or potential energy difference.

- OPB:*Portion of entropy* — A thermodynamic entity that is the extent that a process is thermodynamically reversible.
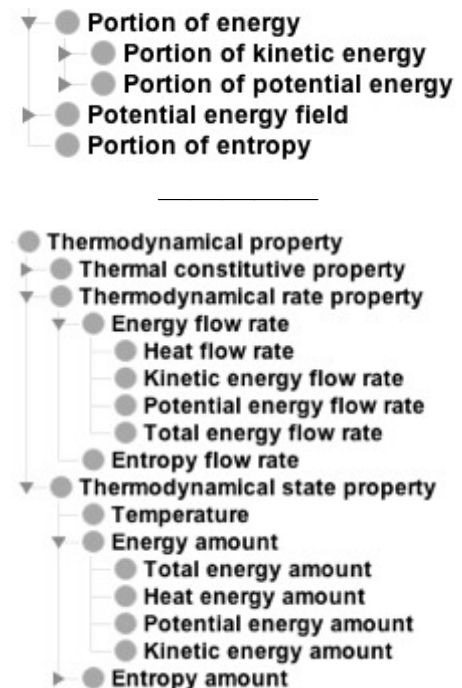

Figure 8 . OPB classes that define thermodynamical entities (top). OPB:Thermodynamic property classes (bottom) that represent amounts and flow rates of energy, entropy, and energy fields.

Although thermodynamic quantities and terms are invoked technically ("horsepower", "solar energy") and colloquially ("feel the

burn"), in fact thermodynamic quantities and flows are themselves invisible and, per Feynman, are defined and quantified solely as mathematical functions. Yet the "reality" of thermodynamic energy is hardly debatable. First, thermodynamic energy is a conserved quantity just as is matter. Second, thermodynamic laws apply universally across all spatiotemporal scales from subatomic particles, to biological organisms, to astrophysics.

The utility of thermodynamics-based dynamical analysis has long been appreciated (17, 20, 21) and has recently received computational support as multidomain biophysical modeling using so-called "bond graph theory" (16). Thus, we have recently focused on a thorough representation of the entities, properties, and dependencies that represent the foundations of classical thermodynamics.
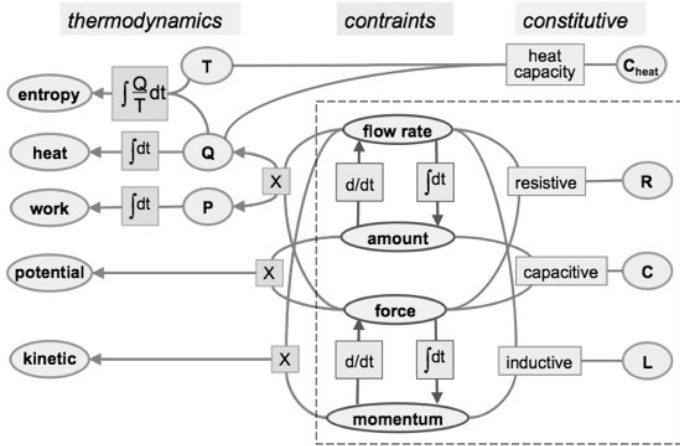

Figure 9. Foundational dependency relations linking OPB:Physical property instances (ovals) to OPB:Physical dependency instances (rectangles) as linked by hasPlayer relations (lines). The content of Figure 4 is repeated inside of the dashed box to show how thermodynamic properties depend on dynamical properties. T = temperature, Q = heat flow, P = work flow. Boxes marked "X" represent simple arithmetic products; e.g., the kinetic energy of a material entity is the product of its flow rate (e.g., velocity) times its momentum.

Building from Figure 4, Figure 9 shows a schematic view of how thermodynamic entities are derived from the more basic ideas of forces, flows, amounts and momenta. Also represented in Figure 9, is that a dynamical flow rate times an applied force is partitioned between flow of heat energy (Q, as for frictional losses) or power (P, useful work rate) depending on the specific physiological mechanism.

> **Issue 2:** *How "real" are energy and entropy given that they are defined and evaluated only by physical dependencies of the values of observable properties?*

OPB:*Dynamical process* as energy flow

The mappings of Figure 9 suggest that a fundamental feature of real biophysical systems is that nothing happens or occurs without the flow and dissipation of energy. As a simple example, consider an elastic basketball that is dropped from some height. As the ball accelerates toward the ground, its gravitational potential energy (proportional to its elevation) is converted to kinetic energy (pro-

portional to its momentum times velocity; as in Figure 9). On impacting the pavement, the accumulated kinetic energy is converted to elastic potential energy as the ball and the earth are deformed by contact forces. Once deformation is complete, then the elastic forces accelerate the ball upwards as the elastic potential energy is converted to kinetic energy. The cycle of falling and rebounding would be perpetual but for the friction of air flow around the ball with consequent heat dissipation and entropy production.

These entities and relations are the basis for analyzing multiscale, multidomain processes throughout biomedicine from molecular biophysics to cardiovascular function to skeletal biomechanics. The overriding principle is that nothing flows, moves, accelerates, or changes shape without the flow and dissipation of energy. This observation has suggested to us a biophysics-based definition of OPB:*Dynamical process* as "A physics occurrent that is the flow or exchange of matter and/or energy amongst dynamical entities that are participants in the process."

The broad notion is that biological continuants are physical things that change <u>only</u> by virtue of the flow and dissipation of energy. Whether material entities are being synthesized, participating in processes, or are being degraded, energy is flowing and being dissipated (as entropy as in Figure 9). Even in a steady-state situation during which there are no changes in, say, chemical concentration, muscle length, or blood flow rate, energy is flowing and being dissipated. This definition is *inclusive* because it applies to all manner of physical participants in all physical domains and scales. It also satisfies the notion that no real physical process can occur without the flow and expenditure of energy (OPB:*Portion of energy*) with an attendant increase of entropy (OPB:*Portion of entropy*).

Each dynamical process class specifies the structural class of each process participant, the specific dynamical properties of each process participant, the dependencies (e.g., physical law) amongst those properties, and flow rates of energy that constitute the process. This is a fine-grained, physics-based approach that we use to identify, annotate, and reason over biophysical mechanisms as computationally modeled in the Physiome and other projects (11, 12, 13). Key subclasses of OPB:*Dynamical process* are shown in Figure 10.
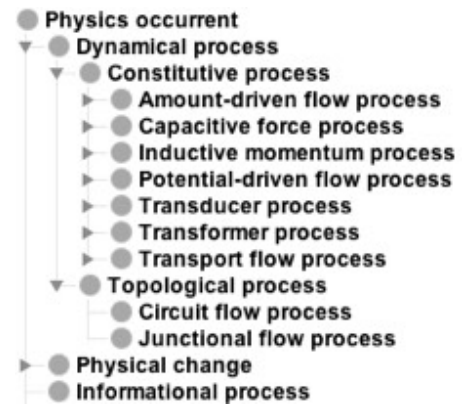

Figure 10 . OPB:Physics occurrent classes

> **Issue 3:** *Can the OPB's system dynamical perspective rationalize and simplify the classification of biological processes according to energy types and flows?*

Discussion

The OPB is an ontology of classical physics as applied to problems in biomedical research, biophysical analysis, and mathematical modeling. It represents foundational aspects of classical physics, engineering system dynamics, and thermodynamics of biological entities, systems and their processes. Whereas it takes inspiration from the "realist" representational framework of the BFO, it expresses and formalizes principles of system dynamics and thermodynamics that are the bases of dynamical analysis of biological processes.

The OPB builds on and extends the "realist" ontological foundations of BFO to represent classical physics as a computational ontology. We routinely computationally integrate OPB and BFO-based OBO ontologies to annotate and compute across the continuants, processes, and physical properties of biophysical models (12, 13, 14). Thus, we can demonstrate computational compatibility of BFO and OPB.

However, we are concerned with ontological incompatibilities that exist when representing physical entities, physical properties, and the laws of classical physics in the context of BFO realism. We have four concerns as raised in prior sections and relate them to those raised by Lord and Stevens (15).

OPB:*Physical property* classes include temporal, spatial, and spatiotemporal derivatives of physical property values.

Such mathematical functions are absolutely critical to the representation and analysis of dynamical physical systems, beginning with the definition of "velocity" as the differential rate of change of position per unit time at any instant in time. A central concept from calculus, per Newton and Leibniz, is to reframe the definition so that the velocity at a point in time (or place in space) is the *limit* of the ratio of $\Delta x / \Delta t$ as Δt approaches zero duration. Conversely, the change of location (Δx) of an entity is the temporal integral $\Delta x = \int v dt$ over a span of time Δt. Generalizations of such calculus-based quantitative relationships pervade all manner of analytical modeling systems, both as ordinary differential equations (ODE) and, more generally, as partial differential equations (PDE). OPB offers these classes not as actual computations on the property values but simply as qualitative dependencies so that, for example, a derivative computation in a mathematical model (e.g., dx/dt) would have a positive value if the value x was calculated to increase over a time interval. Lord and Stevens (15) offer additional examples of differentials that have no representation in realism.

OPB:*Dynamical dependency* classes represent quantitative dependencies of physical property values upon each other according to constraint axioms and laws of physics.

The OPB:*Dynamical dependency* classes represent all manner of rules, observations, intuitions, or hard-and-fast physical laws. As a simple example, a dynamical dependency instance can represent an empirical finding that when a patient consumes more carbohydrate their blood glucose level increases for a span of time. From this observation, one might derive a mathematical model that approximates the observed changes using an analytical model that also represents an (empirical) dependency of blood glucose on the rate of sugar uptake into the blood.

Some dependencies are instances of OPB:*Conservation dependency* that express fundamental axioms such as for conservation of mass or energy. Others constraints are instances of OPB:*Constitutive dependencies* that represent empirically observed dependencies such as for "Ohm's Law" which is a relationship between an electrical current (I) and the electrical voltage (V) across an electrical conducting pathway (see Figure 4). In an "ideal" case, Ohm's law represents I-V relations as *linear*, as for electrical circuits elements. However, the I-V constitutive dependency of cell membrane ion channel current flow is usually quite *nonlinear* as well as *time-dependent*. In OPB such specific cases are representable as subclasses of OPB: *Dynamical dependency*.

OPB:*Thermodynamical entity* and *dependency* classes represent thermodynamic properties and property value dependencies according to the laws of thermodynamics.

One key issue between classical physics and BFO realism is that from the perspective of physics, *thermodynamic energy* appears to be just as "real" as matter in that: 1) both are subject to a universal law of conservation and can be neither created nor destroyed, and 2) the amount of each is fully determined by mathematical functions of the values of other dynamical properties as mapped in Figure 9.

Although the formal, quantitative definitions of thermodynamic quantities (e.g., heat, work, entropy, kinetic energy) are less familiar than dynamical quantities (velocity, amount, momentum, etc.), thermodynamical analyses have profound power for representing and constraining dynamical analyses. Thus, important modeling approaches have included these concepts (16, 17, 18, 21).

A major concern for representing thermodynamic energy in a realist context is that because it can be neither created nor destroyed (i.e., conserved) it would seem to be some kind of BFO:*Continuant* and more specifically, an instance of BFO:*Immaterial entity* such as a spatial region of 0, 1, 2, or 3-dimensions. However, two issues arise when considering energy entities with respect to the BFO stricture that all spatial entities are spatially bound. First, potential energy fields such as for gravitional potential or electrical potential fields can extend spatially without limit. Second, it is not clear just where the energy in a field resides as it exists only by virtue of a displacement of charge or material within the field.

> **Issue 4:** *How "real" are physical laws that consist entirely of mathematical functions of the values of observable physical properties?*

OPB:*Dynamical processes are defined as the flow energy or information amongst participants in such processes.*

Every biophysical process, whether a molecular reaction, a flow of blood, or exocytosis of a hormone granule occurs because it is energetically favorable to do so and will stop if the energy sources are depleted. This simple notion is pervasive for all scales and domains and applies as well to muscle flexion as to glucose phosphorylation. We therefore define physical processes as the flow of thermodynamic energy. This notion offers attractive features by providing a means to: 1) calculate an energy expenditure for each process according to, say, metabolic energy output and contractile energy consumption, 2) trace causal pathways according to how energy is exchanged amongst system components. We have begun to implement this idea by defining OPB:*Dynamical process* as "A physics occurrent that is the flow or exchange of

matter and/or energy amongst dynamical entities that are participants in the process."

Conclusion

We have reviewed our implementation and use of the Ontology of Physics for Biology with an eye to maintaining as much consistency as possible with the realist orientation of the Basic Formal Ontology (BFO). However, whereas the OPB has benefitted greatly from the BFO formalism, there are concepts central to the representation of classical physics that are difficult to fit into the realist perspective. Consequently, we consider the OPB to be an orthogonal companion ontology to BFO. Given wider use and maturity of the evolving OPB, we seek to enhance BFO-OPB interoperability in support of semantic annotation, logical inference, and quantitative analysis of complex, multiscale, multidomain biological systems.

Address for correspondence

Corresponding author: Daniel L. Cook (dcook@uw.edu)

References

1. Hodgkin, A.L. and A.F. Huxley, A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol, 1952. 117(4): p. 500-44.
2. Michaelis, L., et al., The original Michaelis constant: translation of the 1913 Michaelis-Menten paper. Biochemistry, 2011. 50(39): p. 8264-9.
3. Crampin, E.J., N.P. Smith, and P.J. Hunter, Multi-scale modelling and the IUPS physiome project. J Mol Histol, 2004. 35(7): p. 707-14.
4. Hunter, P., et al., Integration from proteins to organs: the IUPS Physiome Project. Mech Ageing Dev, 2005. 126(1): p. 187-92.
5. Fenner, J.W., et al., The EuroPhysiome, STEP and a roadmap for the virtual physiological human. Phil. Trans. R. Soc. A, 2008. 366: p. 2979-2999.
6. Arp, R., B. Smith, and A. Spear, Building Ontologies with Basic Formal Ontology2015, Cambridge, MA: The MIT Press.
7. Cook, D.L., F.L. Bookstein, and J.H. Gennari, Physical Properties of Biological Entities: An Introduction to the Ontology of Physics for Biology. PLoS ONE, 2011. 6(12): p. e28708.
8. Cook, D.L., et al., Ontology of physics for biology: representing physical dependencies as a basis for biological processes. Journal of Biomedical Semantics, 2013. 4(12): p. 41.
9. Borst, P., H. Akkermans, and J. Top, Engineering ontologies. Int. J. Human–Computer Studies, 1997. 46: p. 365-406.
10. Gruber, T.R. and G.R. Olsen. An Ontology for Engineering Mathematics. in Fourth International Conference on Principles of Knowledge Representation and Reasoning. 1994. Gustav Stressman Institut, Bonn, Germany: Morgan Kaufmann.
11. Cook, D.L., et al. HeartCyc, a cardiac cycle process ontology based in the Ontology of Physics for Biology. in 2nd International Conference on Biomedical Ontology (ICBO-2011). 2011. Buffalo, NY.
12. Neal, M.L., D.L. Cook, and J.H. Gennari. An OWL knowledge base for classifying and querying collections of physiological models: A prototype human physiome. in International Conference on Biomedical Ontology 2013 (ICBO2013). 2013. Montreal, Ont, CA: CEUR-WS: 24-Nov-2013.
13. Neal, M.L., J.H. Gennari, and D.L. Cook. Qualitative causal analyses of biosimulation models. in International Conference on Biomedical Ontology and BioCreative. 2016. Corvallis, OR, USA: CEUR-ws.org Volume 1747.
14. Neal, M.L., et al., Semantics-Based Composition of Integrated Cardiomyocyte Models Motivated by Real-World Use Cases. PLoS One, 2015. 10(12): p. e0145621.
15. Lord, P. and R. Stevens, Adding a little reality to building ontologies for biology. PLoS One, 2010. 5(9): p. e12258.
16. Gawthrop, P. and E.J. Crampin, Bond Graph Representation of Chemical Reaction Networks. IEEE Trans Nanobioscience, 2018. 17(4): p. 449-455.
17. Karnopp, D., Bond graph techniques for dynamic systems in engineering and biology,1979, New York: Pergamon Press.
18. Le Rolle, V., et al., A bond graph model of the cardiovascular system. Acta Biotheor, 2005. 53(4): p. 295-312.
19. Feynman, R., The Character of Physical Law1994: Modern Library.
20. Perelson, A.S., Network thermodynamics. An overview. Biophys J, 1975. 15(7): p. 667-685.
21. Beard, D.A., A Biophysical Model of the Mitochondrial Respiratory System and Oxidative Phosphorylation. PLOS Computational Biology, 2005. 2(1).