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HeartCyc, a Cardiac Cycle Process Ontology Based in the Ontology of Physics for Biology

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Abstract. The computational representation of biological process knowledge is fundamental to post-genomic biomedical research and clinical practice; yet there is little agreement as to how to define and classify such processes. Here we offer a physics-based ontological schema for defining and encoding biological processes in terms of the temporal intervals during which they occur and the physical properties of participating physical entities. We develop and illustrate the use of the Ontology of Physics for Biology framework by encoding the HeartCyc ontology that represents the cardiac cycle as a multiscale use-case that spans multiple biophysical domains. We discuss the significance of our physics-based approach for rigorously defining biological processes and for bridging the disparate fields of biomedical ontology and biosimulation.

Keywords: Ontology, biophysics, thermodynamics, processes, cardiac cycle

1 Introduction

Biomedical research and clinical practice depend on measuring and describing biological processes, normal and abnormal, that occur in human and non-human organisms. In the post-genomic era, the computational encoding and sharing of such knowledge increasingly depends on controlled vocabularies and biomedical ontologies as resources for defined terms and computational models. Whereas the physical participants in biological processes (genes, proteins, cell types, organs, etc.) are encoded and cataloged in a growing collection of terminologies (e.g., ChEBI [1], UMLS [2], SNOMED-CT [3]) and biomedical ontologies (e.g., FMA [4], GALEN [5], Gene Ontology (GO [6])), the biological processes themselves are only scantily and informally represented.

For example, Gene Ontology's (GO) Biological Process ontology defines "heart contraction" (GO:0060047) as the "...process in which the heart decreases in volume in a characteristic way to propel blood through the body." Whereas this statement describes some occurrences during cardiac contraction, it lacks the detail, structure, and rigor of process knowledge formally encoded in quantitative mathematical models of cardiac mechanics and blood flow (e.g., [7-10]). Our goal has been to develop semantics and ontological methods by which the biophysical content of such models—the physical participants, underlying biophysics, and process knowledge—can be made available in logical form. To develop and test these methods, we have heretofore, focused on annotating and merging biosimulation models [9, 11, 12], most recently in the context of the European Union Virtual Physiological Human project (VPH [13])—a large-scale, international effort to integrate and connect biomedical data with bio-simulation models.

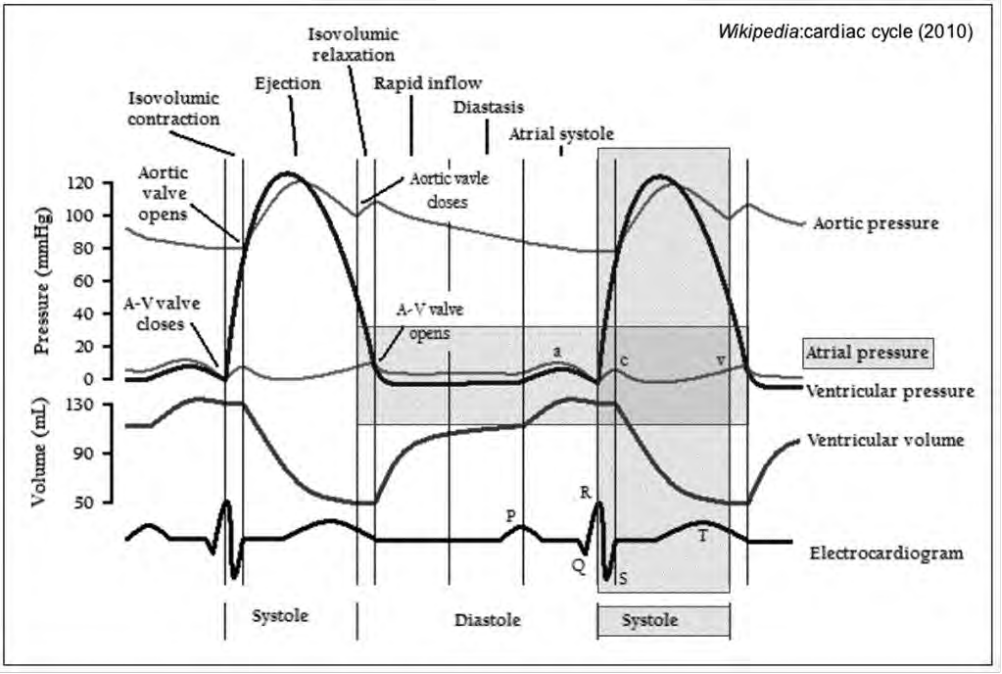

Figure 1. A Wiggers diagram graphically represents the cardiac cycle as could be recorded during a physiological experiment, as computed by a biosimulation model, or as explained to a student. Observable physical properties are labeled on the right (with calibrated scales on the left). Various temporal intervals are labeled at the bottom and top. The "cross-product" of "Atrial pressure" and "Systole" interval is high-lighted as discussed in the text.

2 Resources and Ontological Approach

2.1 Domain Knowledge: Biophysics of the Cardiac Cycle

We chose the cardiac cycle as a use-case because it is a clinically important process that has been taught to generations of physiologists and physicians and is the focus of continuing research and computational modeling in health and disease. The cardiac cycle presents a number of representational challenges as it occurs at multiple spatial and temporal scales and spans multiple biodynamic domains. For example, over the time course of seconds ventricles contract and blood flows, while on a millisecond time scale myofilaments contract triggered by fluctuations in intracellular calcium ion levels.

Although our approach to encoding biological processes is intended to generalize to all spatiotemporal scales, we here describe our HeartCyc ontology that encodes the temporal changes in physical property value during the cardiac cycle as displayed in a "classical" Wiggers diagram (Figure 1).

2.2 HeartCyc Implementation and Source Ontologies

HeartCyc is encoded in OWL[1] using the Protégé 4.1 ontology editor. We have implemented the HeartCyc ontology using classes and relations from three source ontologies:

- The Ontology of Physics for Biology (OPB [11, 14]) provides the root classes that are extended to encode HeartCyc classes that are specific to the cardiac cycle use-case. OPB classes are designated by an "opb:" prefix. HeartCyc subclasses that extend OPB carry a "heartCyc:" prefix.
- The Foundational Model of Anatomy (FMA [4, 15]) is the source of anatomical structural knowledge of the heart and those parts that participate in the cardiac cycle. FMA classes carry an "fma:" prefix.
- The Relation Ontology (RO [16]), and the

[1] Technically, there are some challenges to representing this knowledge in OWL-DL. These technical details are outside the scope of this paper, and orthogonal to our argument.

OBO Process Ontology [17], provide standardized relations such as ro:*part_of,* ro:*has_participant*, and ro:*preceded_by* to encode relations between ontology classes. Relations Ontology classes carry the "ro:" prefix.

3 HeartCyc: An Ontology of the Cardiac Cycle

To introduce the HeartCyc ontology, we describe four key aspects of our representational approach to features displayed in the Wiggers diagram. *First*, we describe observable physical properties such as "Atrial pressure". *Second*, we describe temporal entities such as the interval "Systole". *Third*, we describe state trajectories and state events that are cross-products of properties and temporal intervals. *Lastly*, we define dynamic processes as thermodynamic entities that are manifested by state trajectories and events. We discuss how this approach generalizes to other process domains and how it supports the temporal and structural decomposition of physical processes.

3.1 Properties of Physical Entities that Participate in the Cardiac Cycle

The first task is to encode a HeartCyc class for each of the physical properties that are named along the right hand side of the diagram. Each such property is a subclass of OPB:*Dynamical property* that is related to a physical entity by an OPB:*physical_property_of* relation. Encoding "Atrial pressure" and "Electrocardiogram" as examples, we have (shown as RDF triples):

- {<heartCyc:Pressure of blood in aorta>
  <rdfs:subClassOf>
  <opb:Fluid pressure>}
  {<heartCyc:Pressure of blood in aorta>
  <opb:physical_property_of>
  <fma:Blood in aorta>}
- {<heartCyc:Electrocardiogram potential>
  <rdfs:subClassOf>
  <opb:Electrical potential>}
  {<heartCyc:Electrocardiogram potential>
  <opb:physical_property_of>
  <fma:Body surface>}

During the cardiac cycle physical processes have cellular and molecular participants for which there is no single FMA class. For example, a multiscale Wiggers diagram could include "Intracellular Ca^{++} concentration of ventricular myocyte" as a physical property (an opb:*Chemical concentration*) that must be composed from classes in other biomedical ontologies using RO structural relations. We encode such annotations as "composite annotations" as previously described [12].

Dynamical properties are not, of course, independent of each other. Rather, their values change according to physical laws. For example, the pressure and volume of the left ventricle depend upon each other according to a volumetric version of Hooke's law. Aortic valve flow rate depends on the ventricular/aortic pressure difference and the valve's fluid flow resistance according to Ohm's law for fluids. We have developed and use semantic methods (SemGen [9, 18]) for encoding such physical properties and dependencies as semantic networks that can be decomposed and recomposed according to physical principles.

In addition to biophysical decomposition, as above, properties may be decomposed (or composed) from other properties according to structural knowledge encoded in the FMA. Thus, one could query an extended HeartCyc, for example, to discover that a property of the left ventricular wall is also a property of the heart according to the FMA's partonomy taxonomy.

3.2 Temporal Intervals that Occur During the Cardiac Cycle

The next step for HeartCyc is to encode classes for each temporal interval (e.g., "Systole") and each temporal instant (e.g., "Aortic valve opens"[2]) as labeled at the top and bottom of Figure 1. We assume that the "Systole" and "Diastole" intervals refer to processes of the left ventricle rather than of the right ventricle, or of atria (e.g., "Atrial systole"). Thus, for "Systole", "Diastole" and the entire cardiac cycle interval (systole + diastole) we can encode a subsumption hierarchy:

[2] A process (e.g., valve opening) may be modeled on one time-scale as occurring in a temporal instant, yet may be modeled on another time-scale as occurring in a temporal interval.

- opb:*Temporal entity*
  - opb:*Temporal interval*
    - heartCyc:*LV systole interval*
    - heartCyc:*LV diastole interval*
    - heartCyc:*Heart cycle interval*

According to Figure 1, temporal intervals (opb:*Temporal interval*) are demarcated and bounded by temporal instants (opb:*Temporal instant*). For example, "Diastole" ends and "Systole" begins at the instant that the "A-V valve closes" and the "Systole" interval ends (and Diastole begins) at the instant that the "Aortic valve closes". Thus, HeartCyc encodes heartCyc:*A-V_ValveCloses instant* and heartCyc: *AorticValveCloses instant* as subclasses of opb:*Temporal instant*.

The temporal relations of these intervals and instants can be encoded by structural relations to encode the part-whole relations of the intervals:

- {<heartCyc:*Heart cycle interval*> <ro:*has_part*> < heartCyc:*LV systole interval*>}
- {<heartCyc:*Heart cycle interval*> <ro:*has_part*> < heartCyc:*LV diastole interval*>}

Intervals and instants can be temporally ordered using the OPB relation opb:*temporally_precedes* so that, for example, the "Aortic valve closes" instant occurs as the temporal boundary between "Systole" and "Diastole":

- {<heartCyc:*LV systole interval*> <opb:*temporally_precedes*> <heartCyc:*AorticValveCloses instant*>}
- {<heartCyc:*AorticValveCloses instant*> <opb:*temporally_precedes*> <heartCyc:*LV diastole interval*>}

The encoding of temporal instants and intervals and their mereotopological relations allows for temporal decomposition of whole processes into temporal parts. With the addition of an axiom that systole and diastole are the only parts of a cardiac cycle (i.e., a closure axiom) then HeartCyc could be queried, for example, to learn that systole and diastole are two parts of a whole cardiac cycle, that they follow each other in a cycle, and that they are separated by the closing of the aortic valve and closing of the A-V valve. This knowledge could be clinically relevant, since certain pathologies are apparent as a disordering of cardiac process intervals and instants. For example, premature ventricular contraction (PVC) is a ventricular systole that occurs prior to atrial systole.

Figure 2. Main subclasses of OPB:*Physical process entity.*

3.3 Trajectories are Cross-Products of Properties and Temporal Entities

The values of a physical property (e.g., values of "Atrial pressure") that occur during an entire cardiac cycle we define as a "state trajectory" which may be demarcated by property state *events* such as the occurrence of landmark property values such as a maximum value, a minimum value, or a value that traverses a designated threshold value. Figure 2 shows OPB classes that encode classes for trajectories and events. Events demarcate temporal boundaries of contiguous temporal intervals as, for example, the heartCyc:*AorticValveCloses instant* could be defined as the traversal of a threshold value in any of several quantitative measures of valve patency (e.g., lumenal area of the valve, the pressure gradient across the valve, or the fluid flow rate through the valve).

Thus, we define opb:*Property state trajectory* and opb:*Property value event* classes as the cross-products of physical properties and temporal entities (i.e., intervals or instants). We also define a class opb:*Physical event trajectory* (analogous to opb:*Physical state trajectory*) that is an temporally-ordered aggregate of property value events that occur during a temporal interval. Physical event trajectories have their own properties such as opb:*Event interval* that is the duration of the temporal interval between two events in the event trajectory.

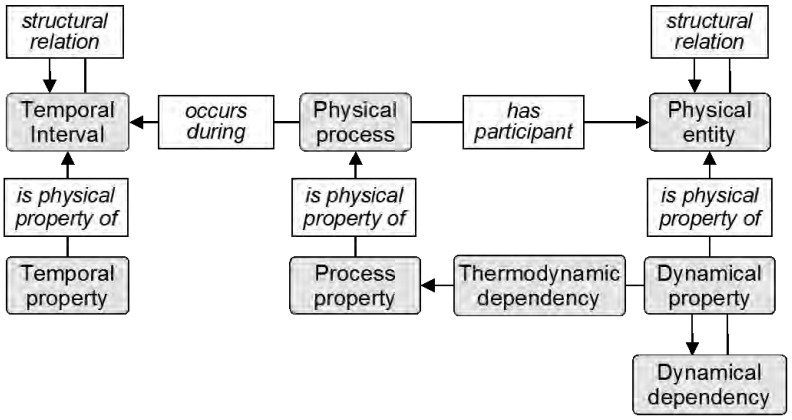

Figure 3. OPB schema for encoding biophysical process ontologies. Physical processes (opb:*Physical process*) have participating physical entities (opb:*Physical entity*) which have physical properties (opb:*Dynamical property*) whose values depend upon one another according to physics-based dynamical dependencies (opb:*Dynamical dependency*). Thermodynamic dependencies (opb:*Thermodynamic dependency*) define thermodynamic energy flow rates (opb:*Process property*) as functions of dynamical properties.

3.4 Physical Processes are Thermodynamic Entities

We have demonstrated that HeartCyc can encode the properties, intervals, and trajectories that occur during a cardiac cycle. In prior work, we have demonstrated SemSim semantic models that encode networks of physical properties linked by of physics-based dependency relations. However, neither of these approaches defines physical process classes that encode, for example, how the contraction of ventricular myofibrils propels blood through the aortic valve during which molecular-level chemical processes are linked to macroscopic fluid dynamic processes.

Our hypothesis is that thermodynamics, a set of physical principles that transcend spatiotemporal scales and physical domains, provides a unifying framework for formally defining, quantifying, and encoding biological dynamical processes. Thus, we propose to define opb:*Dynamical process* as "...the flow, control, transformation, or dissipation of thermodynamic energy within or between participating energetic physical entities according to a physical dependency". This view posits that the occurrence of biological processes is necessarily attended by the flow and dissipation of thermodynamic energy [19, 20] that are described by the laws and axioms of classical physics. As shown by Figure 3, these ideas are captured in the OPB schema for biological processes that relates the dynamical properties of physical entities to process properties that are the energy flow rates that occur during a process due to changes in dynamical property values.

The cardiac cycle clearly qualifies as an opb:*Dynamical process* because its biological participants (the heart, its parts, and their contents) participate in an overall cardiac contractile process that includes a set of linked processes:

- the *transformation* of myocardial chemical energy into myocardial mechanical strain energy,
- the *transformation* of myocardial strain energy into fluid pressure energy of ventricular blood, and
- the *transformation* of ventricular fluid pressure energy into kinetic energy of aortic blood flow.

There are several appeals to this thermodynamic hypothesis. First, it yields to intuitive, qualitative notions of "energy" that serve well for envisioning and encoding processes yet each such process can be rigorously defined and quantitatively validated for data sets and biosimulations. Second, energy is the "common currency" of physical processes that applies as well to chemical kinetic systems as to mechanical and fluid flow systems. This offers a reduction in complexity by combining the values of domain-specific physical properties into a common quantity, energy, that reflects the thermodynamic state

of process participants. Third, because energy is a conserved quantity, one can trace the effects of one process, say myofibrillar contraction, through complex systems to determine effect on other entities, such as ventricular blood flow—"follow the energy".

4 Summary and Discussion

We have developed and here demonstrate a prototype ontology for formally encoding dynamic biological processes as a complement to ontologies of static biological structures. We recognize that we have not evaluated our ontology but simply demonstrated how our prototype HeartCyc ontology could be used to encode key concepts in a Wiggers diagram. Thus, opb:*Physical process entity* classes can be of immediate use to the bioinformatics community for annotating, encoding, and interrelating data sets and model outputs across biomedical domains as required for multiscale integrative projects such as the VPH.

We further distinguish *properties*, *trajectories*, and *intervals* to be "manifestations" of processes rather than being processes themselves. Rather, we posit the need for a unifying theory of biological processes and propose thermodynamics as that theory. By defining physical processes as the conversion and accumulation of thermodynamic energy (for which the temporal trajectories are governed by the laws and definitions of classical physics) we can connect biomedical process ontologies to a rich legacy of prior work in physics-based mathematical models of biological processes.

References

1. Degtyarenko, K., de Matos, P., Ennis, M., Hastings, J., Zbinden, M., McNaught, A., et al., ChEBI: a database and ontology for chemical entities of biological interest. Nucleic Acids Res, 36(Database issue), D344-350, 2008.
2. Unified Medical Language System, http://www.nlm.nih.gov/research/umls/
3. SNOMED CT, http://www.ihtsdo.org/snomed-ct/
4. Foundational Model of Anatomy, http://sig.biostr.washington.edu/projects/fm/
5. Rector, A.L., Rogers, J.E., Zanstra, P.E., & Van Der Haring, E., OpenGALEN: open source medical terminology and tools. AMIA Annu Symp Proc, 982, 2003.
6. Lewis, S.E., Gene Ontology: looking backwards and forwards. Genome Biol, 6(1), 103, 2005.
7. Kerckhoffs, R.C., Neal, M.L., Gu, Q., Bassingthwaighte, J.B., Omens, J.H., & McCulloch, A.D., Coupling of a 3D finite element model of cardiac ventricular mechanics to lumped systems models of the systemic and pulmonic circulation. Ann Biomed Eng, 35(1), 1-18, 2007.
8. McCulloch, A.D., Modeling the human cardiome in silico. J Nucl Cardiol, 7(5), 496-499, 2000.
9. Neal, M.L., Bassingthwaighte, J.B., Subject-specific model estimation of cardiac output and blood volume during hemorrhage. Cardiovasc Eng, 7(3), 97-120, 2007.
10. Noble, D., Modeling the heart--from genes to cells to the whole organ. Science, 295(5560), 1678-1682, 2002.
11. Virtual Physiological Human Network of Excellence, http://www.vph-noe.eu/
12. Cook, D.L., Mejino, J.L., Neal, M.L., & Gennari, J.H., Bridging biological ontologies and biosimulation: the Ontology of Physics for Biology. AMIA Annu Symp Proc, 136-140, 2008.
13. Ontology of Physics for Biology, http://bioportal.bioontology.org/ontologies/44872
14. Foundational Model of Anatomy, http://sig.biostr.washington.edu/projects/fma/release/index.html
15. Rosse, C., Mejino, J.L.V., Jr., (2007). The Foundational Model of Anatomy Ontology. In A. Burger, D. Davidson & R. Baldock (Eds.), *Anatomy Ontologies for Bioinformatics: Principles and Practice* (pp. 59-117). New York: Springer.
16. Smith, B., Ceusters, W., Klagges, B., Kohler, J., Kumar, A., Lomax, J., et al., Relations in biomedical ontologies. Genome Biol, 6(5), R46, 2005.
17. Ozgovde A., Gruninger M., (2010) Foundational Process Relations in Bio-Ontologies. In: Galton A, Mizoguchi R, editors. Formal Ontology in Information Systems: IOS Press.
18. Gennari, J.H., Neal, M.L., Galdzicki, M., & Cook, D.L., Multiple ontologies in action: Composite annotations for biosimulation models. J Biomed Inform, 44(1), 146-154, 2011.
19. Gennari, J.H., Neal, M.L., Carlson, B.E., & Cook, D.L., Integration of multi-scale biosimulation models via light-weight semantics. Pac Symp Biocomput, 414-425, 2008.
20. Neal, M.L., Gennari, J.H., Arts, T., & Cook, D.L., Advances in semantic representation for multiscale biosimulation: a case study in merging models. Pac Symp Biocomput, 304-315, 2009.
21. Peacocke, A.R., (1983). *An introduction to the physical chemistry of biological organization*. Oxford, UK: Clarendon Press.
22. Perelson, A.S., Network thermodynamics. An overview. Biophys J, 15(7), 667-685, 1975.