ABSTRACT

Motivation: The systematic observation of phenotypes has become a crucial tool of functional genomics, and several large international projects are currently underway to identify and characterize the phenotypes that are associated with genotypes in several species. To integrate phenotype descriptions within and across species, phenotype ontologies have been developed. Applying ontologies to unify phenotype descriptions in the domain of physiology has been a particular challenge due to the high complexity of the underlying domain.

Results: In this study, we present the outline of a theory and its implementation for an ontology of physiology-related phenotypes. We provide a formal description of process attributes and relate them to the attributes of their temporal parts and participants. We apply our theory to create the Cellular Phenotype Ontology (CPO). The CPO is an ontology of morphological and physiological phenotypic characteristics of cells, cell components and cellular processes. Its prime application is to provide terms and uniform definition patterns for the annotation of cellular phenotypes. The CPO can be used to make the meaning of terms in a vocabulary explicit. They play a crucial role in the annotation of biomedical data and the integration of model organism databases.

Availability and implementation: The CPO and the code we generated to create the CPO are freely available on http://cell-phenotype.googlecode.com.

Supplementary information: Supplementary data are available at Bioinformatics online.

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1 INTRODUCTION

Phenotype studies on all scales and levels of granularity are now an invaluable tool for functional genomics research. Phenotypes of targeted mutations in animal models are now systematically recorded to reveal the role of individual genes within a biological system. These phenotype studies now play a key role in translational research and are being used to reveal candidate genes for orphan diseases and to identify chemicals that may have effects on these diseases.

The large volume and diversity of phenotypes within different species and across multiple scales and levels of granularity necessitates the application of flexible strategies for managing and integrating data so that it becomes amenable to automated comparative analyses. To integrate biomedical data across heterogeneous information systems, biomedical ontologies are being developed. An ontology is an explicit specification of a conceptualization of a domain and can be used to make the meaning of terms in a vocabulary explicit. They play a crucial role in the annotation of biomedical data and the integration of model organism databases.

Ontologies increasingly rely on the use of Semantic Web technologies. The Semantic Web provides a stack of protocols and languages to include explicit semantics in websites. In particular, the Web Ontology Language (OWL) has been designed to express and share ontologies within the Semantic Web. OWL is a language based on description logics (a group of formal languages based on first-order predicate logic). Automated reasoners have been developed within the Semantic Web to perform complex operations on ontologies formulated in OWL. In particular, automated reasoners can verify an ontology’s consistency and use deductive inference to perform powerful queries over ontologies. To benefit from automated reasoning and the rapidly increasing number of software tools that are being developed within the Semantic Web, most biomedical ontologies are now available in OWL or can be converted into an OWL-based representation.

In the domain of phenotypes, multiple ontologies have been developed. In particular, ontologies to characterize mammalian (Smith et al. 2004), human (Robinson et al. 2008), yeast (Engel et al. 2004), and worm (Schindelman et al. 2010) phenotypes are now available, while several more phenotype ontologies are under development. To benefit from automated reasoning, integrate phenotypes across species and reuse the content of anatomy and process ontologies, we have defined process classes using the framework of the Phenotypic Attribute and Trait ontology (PATO).
The Gene Ontology provides a set of ontologies for molecular and cellular ontologies for qualities, BPs, functions and cell components, and physiology of biological systems can be formally characterized. Attributes can be distinguished so that normal and abnormal phenotypes. We present a theory in which several kinds of process exhibit such a behaviour, and that attributes of processes are often measured indirectly and inferred from other attributes.

Here, we present the foundations for an ontology of process phenotypes. We present a theory in which several kinds of process attributes can be distinguished so that normal and abnormal physiology of biological systems can be formally characterized. We apply this theory to cellular processes and create the Cell Phenotype Ontology (CPO). The CPO is linked to reference ontologies for qualities, BPs, functions and cell components, and its prime application is the unification of phenotypes on the cellular level across different species as well as for annotation of cellular phenotypes in domains in which no such ontologies exist.

2 SYSTEM AND METHODS

2.1 Gene ontology

The Gene Ontology provides a set of ontologies for molecular and cellular biology, originally designed to support structured annotations for genes and gene products in all species with respect to molecular function (MF), BP and cellular component (CC). MF and BP both describe processes, but at a different spatiotemporal scales; in particular, BP includes processes that unfold within cells and within tissues and organs of multicellular organisms. Gene product annotations can be interpreted as identifying participants in the processes.

Over time, GO development has emphasized a normalized approach that includes supplementing existing human-readable text description with formally specified explicit definitions for GO classes. The formalization of GO is readily apparent in its representation of biological regulation.

Regulatory processes may regulate other processes, at either the MF or BP scale or biological qualities. GO accordingly includes three broad categories of regulation terms, regulation of MF, regulation of BP, and regulation of biological quality. The first two are explicitly defined entirely with respect to other GO terms, whereas the third comprises classes in which the regulated qualities are specified by terms from PATO (see below) or anatomy ontologies.

All GO regulation terms use one of three relations, regulates, negatively_regulates and positively_regulates, to link regulation terms to process or quality terms. The regulates relations are defined in terms of qualities: a regulatory process causes a change in magnitude to some quantity, which in turn has an effect on the frequency, rate or duration of some other type of process. Effects that result in increases and decreases quality, which in turn has an effect on the frequency, rate or duration of some other type of process. Effects that result in increases and decreases quality, which in turn has an effect on the frequency, rate or duration of some other type of process.

2.2 PATO and the EQ model

PATO was envisaged and designed to provide a platform for allowing the integration of quantitative and qualitative phenotype-related information across different domains, levels of granularity and species types. PATO is an ontology of phenotype qualities that form basic entities that we can perceive and/or measure such as colours, sizes, rates etc. One of its classification axes is based on the basic type of entity to which a qualities belongs, and PATO distinguishes between qualities of physical objects and quantities of processes.

PATO allows for the description of affected entities by combining various ontologies that describe the entities that have been affected, such as the various anatomical ontologies, GO (Ashburner et al. 2000), the Cell Type Ontology (Hafner et al. 2009), SO (D’Erfio et al. 2008), etc with the various qualities it provides for defining how these entities were affected. PATO can be used for annotation either directly in a so-called post-composed (post-cooking) manner or for providing formal (logical) definitions (equivalence axioms) to ontologies containing a set of precomposed (precoordinated) phenotype terms. For instance, to describe the decrease in the length of the sexual cycle of female animals, we can combine the PATO term Decreased duration (PATO:0000499) with the Gene Ontology term Estrous cycle (GO:0042698), while if such a term is defined in a precomposed ontology (for example, the SP:0009007 term from the Mammalian Phenotype) it could be used to provide an equivalence statement between that class and the above PATO-based description.

2.3 Axioms for physiology phenotypes

We implement our theory of physiology phenotypes using OWL, a formal language based on description logics. Using OWL, we formulate axioms that can be used by automated reasoners to infer additional information. Automated reasoning and the axioms we provide are intended to satisfy three aims. First, we use the axioms to infer information from background knowledge. In particular, we aim to automatically generate a class hierarchy of physiology phenotypes when an ontology of physiological processes, such as the GO, is provided as background knowledge. Our second aim is to provide interoperability with phenotype ontologies of other domains, including species-specific phenotype ontologies that have been formalized using the EQ method. Finally, our third aim is to query physiology phenotypes based on physiological processes that are affected or based on the way in which they are affected.

Our three aims rely on the possibility of using automated reasoning over a resulting ontology of physiology phenotypes. However, OWL is an expressive formal language, and automated reasoning in OWL has a high computational complexity (reasoning in OWL 2.0 is 2EXPTIME-complete). Consequently, due to the exponential increase in worst-case time complexity for automated reasoning in OWL, we would not be guaranteed to achieve our aims once we consider more than very few phenotype classes. In particular, using an ontology of the size of GO, with more than 22,000 classes for processes, as a foundation for constructing an ontology of physiology phenotypes would not allow us to achieve our aims through automated reasoning.

The OWL EL profile is a subset of OWL that significantly decreases the expressiveness of OWL and the resulting time complexity of automated reasoning (Horst et al. 2008). Highly efficient automated reasoners have been developed for OWL EL, which are capable of processing very large ontologies (Horst et al. 2008). To achieve our aims and use automated reasoning for large ontologies, we limit ourselves to the OWL EL profile. As a consequence of the restriction to OWL EL, we cannot make use of not(negation), disjunction (or), universal quantification (forall) and several other types of operations in our axioms (Horst et al. 2008).

The lack of expressivity in OWL EL requires a formulation of axioms so that the inferences we desire (i.e. the subclass relations resulting in the ontology’s taxonomy) are maintained without using features of OWL that go beyond OWL EL expressivity. Consequently, we formulate abnormality and absence similarly to current formalizations of EQ-based...
We develop a model of process attributes that is applicable for retaining certain kinds of attributes, others cannot. Examples of processes occur within infinitesimally small time intervals. Mathematically, this process of subdivision can be iterated until lower frequency processes and qualities of their participants, and include that characterizes the temporal extent of a process and is similar processes' temporal extension. For example, a duration is an attribute include the first are process attributes that arise directly from processes and we distinguish between three different kinds of process attributes: heart may beat rhythmically or arrhythmically within a period of.

3 RESULTS
3.1 Attributes of processes
We develop a model of process attributes that is applicable for representations of physiology and related phenotypes. In principle, we distinguish between three different kinds of process attributes: the first are process attributes that arise directly from processes and include Duration and Temporal location; the second are attributes that arise from processes and their temporal parts and include Frequency and Onset; and the third are attributes that arise from processes and qualities of their participants, and include Flow rates. Attributes that can be directly linked to a process arise from processes’ temporal extension. For example, a duration is an attribute that characterizes the temporal extent of a process and is similar to Length, Area and Volume for one-, two- and three-dimensional physical objects. A Temporal location positions the time interval at which the process occurs with respect to a reference coordinate system.

However, the majority of attributes that characterize processes are not based on these types of process attributes alone, but rather relate attributes of process participants with the duration of a process. In particular, a Rate typically refers to an attribute of some entity with respect to an attribute of another entity, and in the context of processes, rates often refer to attributes of a process participant with respect to the duration of the process. For example, a Mass flow rate refers to the Mass of a process participant with respect to the Duration of the process, that is, how much matter is moved (from one point to another) through the process. As a more complex example, a Rate of change of position refers to the Distance that an object is moved with respect to the Duration of the process.

However, not all rates of a process depend on attributes of the process participants. In particular, a Frequency of occurrence or Event rate refers to the number of occurrences of a type of process during a reference process. For example, a Rate of heart beating refers to the number of Heart beating processes that occur within a reference process (e.g. a process in which the heart participates with a duration of 1 min). Further attributes that depend on types of processes with regard to a reference process are distribution patterns, that is, how the occurrences of processes of a particular type are distributed within a reference process. For example, the heart may beat rhythmically or arrhythmically within a period of time (see Fig. 1).

Related to distribution patterns are changing qualities of processes. For example, the rate of heart beating may change (increase or decrease) throughout the course of a reference process. A simple analysis of increasing (decreasing) rates would be that the rate of a heart beating within the first half of a process is lower (higher) than in the second half of the process. To make such an assertion, we divide a process into two temporal parts. Mathematically, this process of subdivision can be iterated until processes occur within infinitesimally small time intervals. Although some processes can be subdivided indefinitely while retaining certain kinds of attributes, others cannot. Examples of processes that can be divided include Continuous movement or Mass flow processes, for which all parts have a Speed or Flow rate attribute. On the other hand, some processes can be subdivided into stages of activity and stages of inactivity (with respect to a particular process type) and cannot arbitrarily be divided. For example, a process of Heart beating has periods of activity in which a heart beat occurs and periods in which no heart beat process occurs. Consequently, not all parts of the process have a Heart rate (Rate of heart beating) attribute.

We may further attribute a Frequency or Rate to an object instead of a process. For example, a heart that beats now with a frequency of 80 bpm, or a car that is moving at a speed of 180 km/h at a particular point in time (e.g. as observed with a speed camera) can be considered attributes of the objects (the heart or the car), not attributes of the processes in which the objects participate. However, these are different kinds of attributes. Rates, when considered as attributes of objects, may be explicitly defined using rates of processes. For example, the heart beating frequency of a particular heart at a time point is the frequency of a reference heart beating process in which it participates. Such a reference process is necessary to obtain a value for a frequency even when no Heart beating process is occurring. However, the frequency is only an attribute of the heart in virtue of such a reference process in which Heart beating is actually occurring. This reference process can be uniquely determined for processes such as Continuous movement, where the rate of an object at a time point is the rate of the infinitesimally small process that occurs around t. The reference process is ambiguous.

Fig. 1. Six examples of processes with non-comparative and comparative process attributes. We assume that the processes labelled a, b, c and d are instances of the class of processes P. On the left side, three regulation processes (of P) are illustrated which exhibit non-comparative attributes. The first process has an attribute of Rhythmic occurrence of P because the instances of P are temporally equidistantly distributed. The second example shows an Arrhythmic occurrence of P, and the third examples shows an Increasing frequency of P. A regulation process with an Increasing frequency of P attribute is a process in which the value of the Frequency of occurrences of P attribute is lower in the first half of the process than in the second half. The right side of the figure illustrates comparative phenotypic descriptions of processes. On the upper right, the normal reference process is shown. The second example illustrates a Late onset of P, i.e. the attribute that P processes begin later than normal processes. Finally, the lower right illustrates a Decreased frequency of P, since fewer processes of the type P occur within the reference process than normal.
for processes such as Heart beating, and the reference process must be explicitly stated.

3.2 Cell phenotype ontology
Although our considerations about process attributes are only the beginnings of a full-fledged theory, we have derived several phenotype formalization patterns and a high-level taxonomic structure of process-based phenotypes. To evaluate our approach, we created the CPO by automatically applying our patterns to the GO.

Phenotypes in the CPO are either based on structural abnormalities or abnormal physiology involving cells or cell components. Structural abnormalities in the CPO are based on GO-CC hierarchy. GO-CC contains 2918 classes for cell parts (including Cell) and extracellular components of cells. For each CC class C in the GO-CC, we create a new class labelled C phenotype in the CPO. For example, for the class Mitochondrion (GO:0005739) in the GO-CC, we create the class Mitochondrion phenotype.

Among the structural phenotype classes, we first distinguish between normal and abnormal phenotypes. An Abnormal phenotype of C is a phenotype of an organism that does not have a normal C as part, while a Normal phenotype of C represents the state in which an organism has a normal C as part.

Among the abnormal phenotypes that we include for all cell components listed in GO-CC, we distinguish Abnormal morphology and Abnormal physiology phenotypes. An Abnormal morphology of C is either the (abnormal) absence of required parts of C, the (abnormal) presence of additional parts, or abnorma qualities of C (Hoehndorf et al. 2010). For example, an Absence of caveolae (MP:0004150) would be a subclass of Abnormal morphology of plasma membrane in virtue of caveolae necessarily being part of the Plasma membrane (GO:0005886).

Abnormal physiology of a cell component refers to abnormal functionality of a cell component. We assume that a functionality of a cell component is (the potential for) a process in which the cell component is (causally) involved. We use the definitions of GO classes that were created based on lexical decompositions of GO class labels (Bada and Hunter 2007; Mungall et al. 2011; Ogren et al. 2004) to identify the processes in which cell components are involved. For example, the definition of the GO class Mitochondrial fission (GO:0000266) is explicitly defined as an Organell fusion (GO:0048285) that results-in-the-division of a Mitochondrion (GO:0005739). Based on this definition, we make the assumption that Mitochondrial fission is one of the functions of a Mitochondrion and that an Abnormality of mitochondrial fission is a subclass of an Abnormality of mitochondrial physiology.

Among abnormal physiology, we distinguish between abnormalities in a single occurrence of a cell component’s functioning and an abnormal pattern of multiple occurrences of a cell component’s functioning. For example, abnormalities in cell division resulting in Aneuploidy refer to abnormalities of Cell division processes, while an Increased rate of cell division refers to an abnormality in the pattern of occurrence of multiple cell division processes. In the CPO, we follow the GO and represent abnormalities in the pattern of occurrence of X as abnormalities of Regulation of X processes. In particular, an Increased rate of cell division is not an attribute of Cell division processes, but rather arises from the collection of all Cell division processes that occur within an organism at a given time. In the GO, Regulation of X processes refer to those processes that determine how often and in which way one or more X processes occur. Therefore, we assign the attribute of Increased rate of cell division to Regulation of cell division processes.

Single occurrences of processes can be abnormal in multiple ways, depending on the type of process. First, common to all processes is the quality of Duration and consequently, each process can have an abnormal (increased or decreased) duration. For example, a part of an organism may participate in an Inflammatory response (GO:0006954) that lasts longer than normal, that is, the organism has an Increased duration of inflammatory response phenotype. We define such a phenotype as a phenotype of an organism which has a part that participates in Inflammatory response, and this Inflammatory response process has an Increased duration (PATO:000498).

The second common type of abnormality are abnormalities based on process participants in relation to the duration of the process. These include all kinds of rates such as Mass flow rate, Energy flow rate and Velocity (the rate of change of position). In each of these cases, an object participates in a process and a quality (or change of quality) of that object throughout the duration of the process is considered to form a new quality. If the process has participants that are distinguished into inputs and outputs, then a recurring pattern is that the amount of inputs or outputs that participate in the process can be increased or decreased. For example, an Increased rate of cytoplasmic streaming can be defined as an increased amount of inputs or an increased amount of outputs of a Cytoplasmic streaming process.

Finally, some objects may be divided into stages during which particular states of affairs obtain, and a process may be abnormal in that these states of affairs do not obtain at a particular stage. Notably, at the beginning and the end of a process, pre- and post-conditions may obtain that are abnormally changed in a process. For example, Aneuploidy—an abnormality during cell division at which the chromosomes do not separate properly between the two cells — may be considered the result of such an abnormality.

We implement the first two types of abnormalities in the CPO. First, as a subclass of each Abnormality of P class, we create Abnormal duration of P, which in turn has Increased duration of P and Decreased duration of P as subclasses. Second, if we are able to identify inputs I(P) or outputs O(P) of the process P in the formal definitions of the GO, we automatically generate Abnormality of I(P) in P as well as Abnormality of O(P) in P. The left side of Figure 3 illustrates the schema of classes we generate for single process abnormalities.

The second type of abnormality in the CPO relate to abnormalities of multiple occurrences of some process X. According to the GO, regulation processes are processes that maintain or modify the occurrence of processes of a particular type. Following this convention, we call an abnormality of multiple occurrences of X Abnormality of the regulation of X.

A first kind of abnormality of regulatory processes are abnormal temporal distribution patterns of a process. In these abnormalities, the way in which processes of a particular kind are temporally distributed is abnormal. The most common abnormal distribution pattern is an increased or decreased frequency, and we use PATO’s frequency class to define Abnormal frequency of occurrence
Although these abnormalities are often highly informative in clinical diagnostics and biological investigations, we usually lack the necessary information that is required to automatically determine meaningful types of abnormal distribution patterns. A second kind of regulatory abnormalities is related to the onset of a process. With respect to a reference process, a particular kind of process may be Delayed (PATO:0000502) or Premature (PATO:0000694). For example, Delayed apoptosis refers to an abnormality of the Regulation of apoptosis in which apoptosis is induced later than normal. We use the PATO quality Offset (PATO:0002324) and its children to characterize regulatory abnormalities in which a process ends prematurely or too late.

Finally, a third kind of regulatory abnormality refers to abnormal rates with respect to a participant of the process that is being regulated. For example, a cytoplasmic flow rate can be increased or decreased not within a single Cytoplasmic streaming process but rather the total cytoplasmic flow rate, as a summation over all cytoplasmic streaming processes that occur within an organism (or a particular anatomical location), is increased or decreased. Although a flow rate of a single Cytoplasmic streaming process is a quality of that process, an increased total cytoplasmic flow rate is a quality of the regulation of Cytoplasmic streaming. In particular, it is possible for an organism to have a normal—or even a decreased—cytoplasmic flow rate in each individual cytoplasmic streaming process while at the same time having an increased total cytoplasmic flow rate due to a large increase in the frequency of occurrence of cytoplasmic streaming processes. Similarly, the frequency of occurrence of cytoplasmic streaming may be normal or decreased while the total cytoplasmic flow rate is increased due to an increased cytoplasmic flow rate in each individual cytoplasmic streaming process. We include total rates as subclasses of regulatory abnormalities in the CPO because these are the attributes of processes that are often measured or observed, while the rates of individual processes are inferred.

3.3 Implementation

We were faced with two choices for implementing the CPO: we could either implement a pre-composed ontology in which all classes and their definitions are pre-generated according to the patterns we define, or we could develop an annotation software that enables the selection of our process phenotype patterns based on the current structure of the GO. To maximize the utility and compatibility of the CPO, and to provide stable identifiers for its concepts, we selected the first strategy and developed a software to automatically generate a pre-composed ontology from the GO.

We developed a software that uses the OWL API (Horridge et al. 2011) to generate an OWL representation of the CPO. The software requires three input files: a version of the GO on which to base the generated CPO, a version of PATO that is used to define abnormal qualities and a copy of the GO cross-product definitions (Mungall et al. 2007) that is used to relate cell components to the processes in which they participate as well as identify the participants, inputs and outputs of processes.

We automatically generate a unique numerical identifier for each class in the CPO. Since the CPO is based on the GO and need to be updated with subsequent versions of the GO, we must ensure to keep identifiers stable in subsequent versions of CPO. Therefore, we use the identifiers for GO classes to generate CPO class identifiers.

In the CPO, identifiers contain two components and are of the form CPO:XX002XXX000, where XX002XXX is the seven-digit identifier of the GO class on which the CPO class is based, and XX is a prefix that identifies the type of phenotype pattern that is applied to the GO class. For example, based on the class Apoptosis (GO:0006915), we generate the CPO classes Abnormality of Apoptosis, Abnormality of single occurrence of apoptosis and Abnormality of regulation of apoptosis. We use the prefixes X2,
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14 and 15 for each of the corresponding phenotype patterns and consequently generate the class identifiers CPO:120006915, CPO:140006915 and CPO:150006915. As long as the GO maintains its identifier for the Apoptosis class, the identifiers in the CPO will remain stable even when it is regenerated.

We use the labels of GO classes to automatically generate class labels for phenotype classes as well as textual definitions for classes in the CPO. For example, the label for the class for increased occurrence of Apoptosis is Increased frequency of occurrences of Apoptosis, and its textual definition states that an increased occurrence of occurrences of Apoptosis is a phenotype of Regulation of apoptosis in which the number of occurrences of Apoptosis within a given time period is increased in comparison to a reference process that is considered normal.

As of November 2011, CPO contains 125,466 classes of which 79,236 are explicitly defined. The ELK reasoner (Kazakov et al., 2011) is able to perform a classification of the ontology in under 10s. We make the ontology and the source code that is used to generate it freely available on http://cell-phenotype.googlecode.com

4 DISCUSSION

4.1 Applications of the CPO

The Fission Yeast Phenotype Ontology (FYPO), a new ontology developed to support annotation of phenotypes in Schizosaccharomyces pombe, consists of pre-composed terms describing normal or abnormal cellular phenotypes. Over 80% of FYPO definitions reference descendants of GO-BP's Cellular process as the entity; a further 11% reference GO-CC terms. All FYPO explicit definitions reference qualities in PATO, including normal, abnormal and several process qualities including Increased duration and Decreased occurrence. FYPO will, thus, fit neatly under the CPO umbrella and stands to benefit from the automated synchronization between CPO and GO, as well as the integration of cellular phenotypes across species that the CPO can provide.  

A further domain that will greatly benefit from the CPO is systems microscopy, which aims to understand complex and dynamic cellular systems by combining automated fluorescence microscopy, cell microarray platforms, quantitative image analysis and data mining (Lock and Strmblad, 2010). If we consider some of the studies, which have been published in this field in the last few years (Pincus et al., 2006; Neumann et al., 2009; Schmitz et al., 2010), the need for CPO becomes evident. In the three studies, live-cell imaging assays and RNAi knockdown were used to generate phenotypic profiles that quantify the cellular response to a given siRNA thus allowing identification of hundreds of genes involved in diverse biological functions including cell division, migration and survival. In each study, several phenotypes were detected and described by the authors without the use of ontologies or controlled vocabularies, making the integration between datasets extremely difficult. For example, it is evident that cell division phenotypes were observed in all three datasets and referred to by terms such as Mitotic delay/arrest, Prolonged mitotic exit, Methaphase delay and Methaphase cells. Without a controlled vocabulary of cellular phenotypes, the overlap between such phenotype descriptions is unclear.

Data integration is also complicated by the lack of standardization at the level of data production and processing; all these issues are currently being address by the different groups involved in the Systems Microscopy Network of Excellence (http://www.systemsmicroscopy.eu/) and the first step towards data integration can be achieved by further developing CPO. This ontology will be used to integrate phenotypes' definitions across existing datasets and will then become an integrated part of the data processing pipeline and used to annotate the data as it gets generated (Conrad et al., 2011).

4.2 Future research

Our main contribution is an analysis of process phenotypes that are used across multiple domains and scales and which are crucial for understanding and representing physiology of living systems. The Ontology of Physics in Biology (OPB) (Cook et al., 2011) is an ontology that has recently been proposed to characterize physiological processes and the physical qualities of biological entities based on a theory of fluid dynamics. It is an important goal for future research to incorporate the OPB in phenotypic descriptions and make our theory of process phenotypes compatible with the physical descriptions of processes and their attributes as outlined by the OPB.

We implemented the CPO using a pattern-based approach to formulating phenotypes involving processes. The patterns we identify are based on pre-existing ontologies; in particular, the PATO ontology and the classification of cellular processes as well as CC in the GO. The result of our method is a large ontology in which classes for phenotypes are pre-composed: they are named and defined within an OWL ontology. However, the large size of the resulting ontology may impair its utility for data annotation and integration, and software tools may not always support such very large ontologies. The alternative to pre-composing all possible phenotype classes using the patterns we describe is to dynamically generate appropriately defined classes at the time at which they are being used. To achieve this goal, software must be developed to support ontology users in applying these patterns and generate the appropriate class description when required.

A further important task is to develop the theory we outlined and applied for the CPO. In particular, a precise formal characterization of this theory in terms of axioms will further improve the clarity of phenotypic descriptions of processes and enable its integration in well-developed formal ontologies of processes (Henz et al., 2009; Ozgevc and Grönnund, 2010).

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