

# Representing and annotating the anatomy of the Virtual Physiological Human: A key to data and model interoperability.

## Abstract

This document outlines the proposal for the Virtual Physiological Human community to adopt a consistent methodology to address anatomical location in the human body, regardless of scale or context. In the long term, this methods framework will also endeavour (i) to organize multi-scale visualization and annotation, as well as (ii) to ensure compatibility with standardized terminologies used in labelling radiological datasets and clinical records.

## Introduction

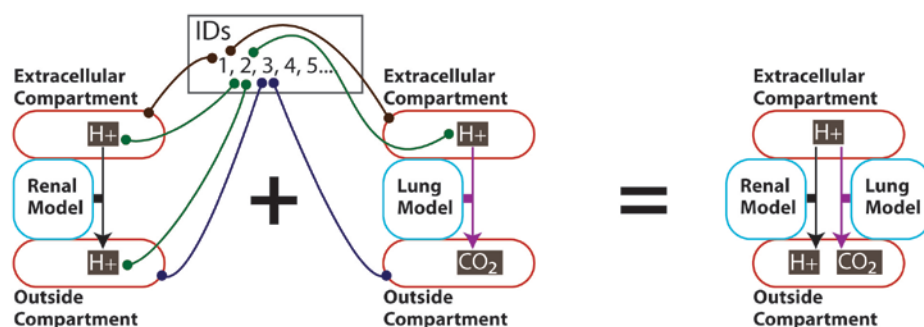
A number of model collections and repositories form part of the Virtual Physiological Human (VPH) network of resources. One of the VPH project's key goals is to support the interoperability of independently created models from these sources. In view of the growing number of disparate VPH models accumulating within its repositories, it is opportune to establish a set of communal annotation and curation standards that would facilitate the automated detection of interoperability potential (*i.e.* compatibility) between models across the whole VPH repertoire.

## Detecting functional model overlap

Models that are able to interoperate may do so because they 'overlap' functionally. How may model overlap be identified? At its most basic level, a definition of overlap may be set as follows:

**Two models overlap if the processes they depict share identical participating structures (*i.e.* have molecules, cellular compartments or other anatomical locations in common).** (1.)

For example, a renal tubular model of acid-base regulation may overlap functionally with a model of alveolar gaseous exchange if  $H^+$  ions in the extracellular compartment are referred to in both processes (Figure 1). Given that this overlap involves directly comparable structures, the scenario depicted in Figure 1 qualifies as an example of 'horizontal integration' between compatible models. Such an operation may only be successfully carried out on models in which participants are labelled in the same ID space.



**Figure 1.** Detecting model compatibility for horizontal integration: Identical structures in different models may be matched up if a common structural ID space is shared.

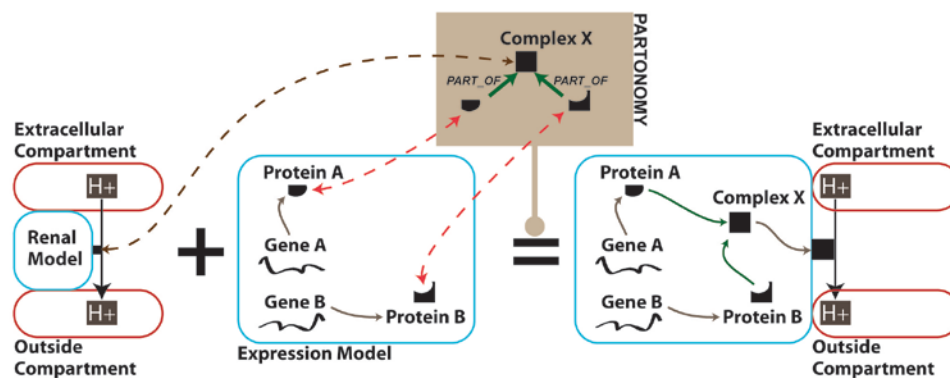
In most cases, however, simple identifier matching may not suffice to detect model compatibility. Interoperability may stem from more subtle structural relationships, other than outright identity, that occur between process participants.

The VPH aim to achieve ‘vertical integration’ of physiological models that interoperate across dimensional scales, for instance, requires methods that detect relationships between biological entities of significantly different size. One such type of relationship might add a second criterion of compatibility as follows:

**Two models overlap if a participating structure in one model is a component of a participating structure in the other model. (II.)**

Model overlap may now be inferred if process participants are known to share a partonomic structural relationship (discussed in [1]). The ‘inference by composition’ defined in (II.) is only feasible if model participant IDs are mapped onto an independent partonomy<sup>1</sup> graph.

The scenario in Figure 2 describes the integration of two models based on the following inference: According to an independent partonomy, the H<sup>+</sup> transporter in the renal model (Complex X) is composed of protein products A and B. These proteins also participate in an expression model that, by inference on this partonomy, describes the production of components of Complex X.

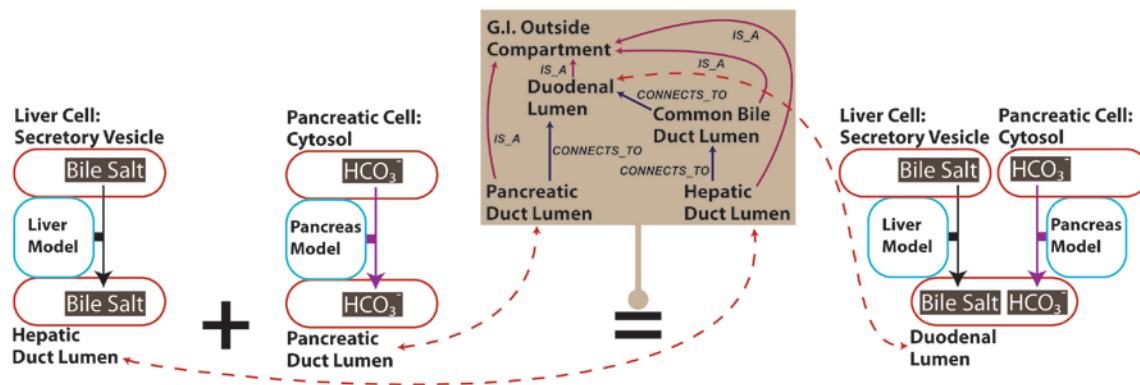


**Figure 2.** Vertical integration of two models achieved via an independent partonomy: the role of the expression model in describing the production of transporter Complex X was inferred from the connectivity of the associated partonomy.

Other relationship types found in structural ontologies permit additional inference strategies to be adopted in model integration. Compartmental connectivity graphs, for instance, may play a key role in functionally linking fluid compartments that are bound by branched structures (*e.g.* vascular, digestive, respiratory or genitourinary tracts). Each adopted type of ontological relationship may require a corresponding definition of compatibility, for example:

**Two models overlap if, given a directed connectivity graph, either (i) a participating fluid compartment in one model is connected upstream to a participating fluid compartment in the other model, or (ii) a participating fluid compartment in one model and a participating fluid compartment in another model are both connected upstream to a third compartment. (III.)**

<sup>1</sup> Partonomy: an ontology graph that connects its nodes with edges representing the ‘PART\_OF’ relationship.



**Figure 3.** Distal integration of two models having structures that share a downstream connection. Note the directed ‘CONNECTS\_TO’ edges indicating direction of flow. The ‘IS\_A’ relationship gathers the various ducts under the same class of the gastrointestinal (G.I.) lumen.

The ‘overlap by connectivity’ scenario depicted in Figure 3 shows a liver model draining into the hepatic duct. According to an independent connectivity graph, this duct empties into the duodenal lumen, which is also downstream to a fluid compartment in the pancreatic model (the pancreatic duct). Despite evident limitations<sup>2</sup>, making use of this type of ontology-based inference may offer new solutions for model integration.

### Proposed course of action

One of the aims of developing of a VPH toolkit is the creation of an accessible communal framework for the interaction of different models in human physiology. Given the growing number of models that are available via VPH-related repositories, supporting the automated large scale matching of functionally overlapping models would be a useful addition to this toolkit.

It is evident, however, that the above approaches to detect interoperability are dependent on a concerted effort of model annotation that the VPH community is as yet to mobilize. To this end, the design of communal modelling annotation standards and guidelines for the VPH is proposed.

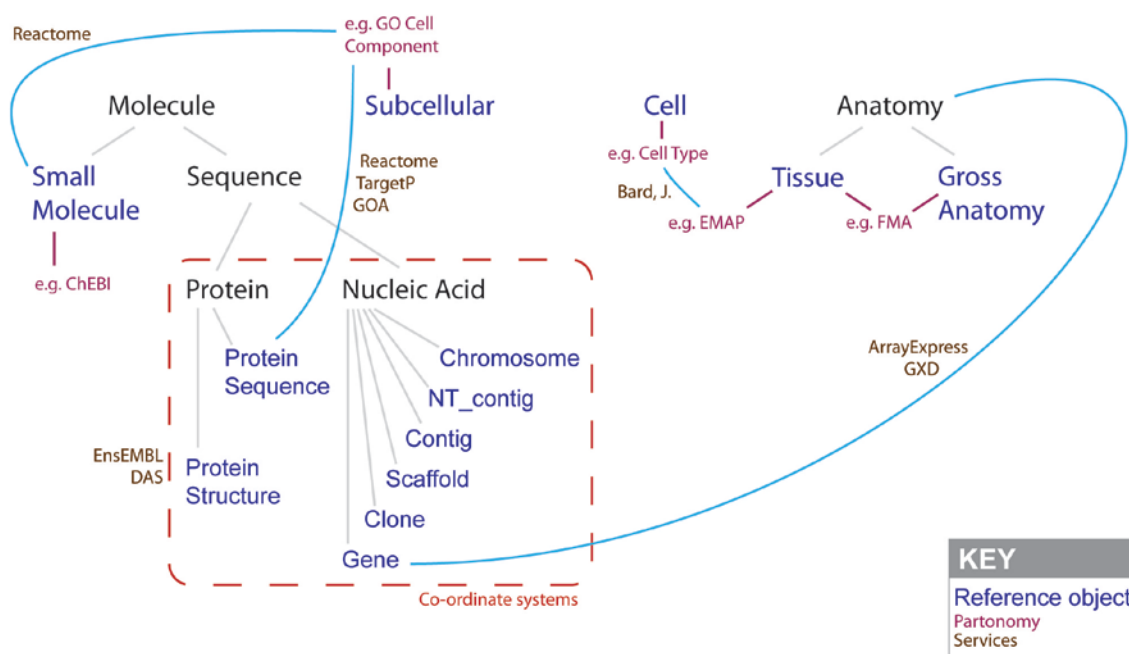
Suggested key stages for this work would include:

- 1) **SURVEY:** The identification and census of structural entities (*i.e.* molecules, cellular compartments or other anatomical locations) that are found in VPH atlases or embedded in VPH models and ontologies.
- 2) **FRAMEWORK SELECTION:** This step aims to provide a communal identifier space to be shared among all structural entities present in VPH resources (identified in (1)). This composite space should be derived from independent structure-based datasets and ontologies that are already well recognized frames of reference in the biomedical domain - this would further promote the interoperability of VPH resources with those established by other biomedical communities. Community-wide consensus is requisite in selecting non-

<sup>2</sup> For example: (i) What is the directional nature of the connectivity that links the gallbladder’s cystic duct with the hepatic and common bile ducts? (ii) May the esophagus be said to be upstream of the stomach if physiological anti-peristalsis (*i.e.* vomiting) is taken into account?

overlapping representative datasets and ontologies that would allow the ID space to extend across the VPH dimensional scales (examples illustrated in Figure 4).

- 3) **CURATION AND FRAMEWORK EXPANSION:** This stage entails the concerted investment of curational resources to:
- a. **Annotate:** tag structural entities in VPH atlases, models and ontologies using stable identifiers from the VPH ID space;
  - b. **Request terms:** collaborate with those independent databases and ontologies at the basis of the VPH ID space to set up a request pipeline that provides stable identifiers for those structural entity terms they are currently missing;
  - c. **Co-ordinate:** work closely with the OBO foundry community [2] to co-ordinate VPH ontology creation, dissemination and maintenance, as well as engaging with the network's ontology-related technology and grant development efforts.



**Figure 4.** A classification of structural reference objects (blue text) of relevance to human biology, showing examples of associated open access paronomies (pink text) and interlinking services (brown text) in the public domain. Ontologies are listed as follows: ChEBI [3], GO Cell Component [4], Cell type [5], EMAP (mouse) [6], and the Foundational Model of Anatomy (FMA) [7]. Some services provide mappings (thick light blue line) between two or more ontologies of structure.

### Long term developments

The co-ordination of annotation and modelling efforts in support of clinically relevant objectives is a central goal to the VPH project. The adoption of a communal structural and anatomical framework by the VPH would promote further development in three key areas that are in direct support of this effort, namely:

- 1) **Visualization:** A multi-scale modelling framework sets the stage for multi-scale visualization methods that draw upon VPH partonomy topologies for their layout. This approach would enable, for example, the systematic illustration of molecular biology data (*e.g.* the impact of gene expression, drugs or mutation on molecular pathways) in an anatomical context. It would therefore be opportune to explore potential interactions with the SBGN/SBML, CellML, BioPAX and other stakeholder communities to collaborate with the VPH on this aspect.
- 2) **Multi-modal annotation:** The development of multi-modal registration methods in radiology has been the main focus of a number of VPH-related projects (*e.g.* [8]). This work has contributed to the creation of statistical volumetric models that represent canonical 3D organ form along with the associated occurrence of regional variation in structure. The use of canonical structures as data templates that can be fitted to patient-specific radiological images opens the possibility of overlaying community-annotated biomedical information onto an individual's anatomy. The discipline of communal annotation of 3D/volumetric data, and the open distribution of such information, has already gained considerable ground in the fields of crystallography [9], electron microscopy [10] and gene expression image-mapping [11]. It may therefore be appropriate for the VPH to co-ordinate anatomy-related ontology development with the creation of an associated atlas of radiological canonical structures (akin to the Protein Data Bank for molecular structures) and initiate efforts for the open, community-based annotation of such templates. Much can be drawn from the Distributed Annotation System (DAS) [12] experience in the management of large scale multi-modal annotation over shared co-ordinate systems (see also Figure 4).
- 3) **Clinical access:** The annotation of electronic medical record systems using clinical terminologies such as SNOMED-CT (<http://www.ihtsdo.org>, [13]) and RADLEX [14] is organizing a wealth of biomedical information in healthcare. A communal structural and anatomical VPH framework would provide a rigorous basis for the further development of human disease ontologies and, in so doing, improve access to associated clinical phenotypic data for basic research. Emerging techniques in quantitative imaging (discussed in (2) above) are also starting to support a more robust approach to clinical phenotyping as patient diagnosis categorization is increasingly based on objective anatomical criteria. However, tangible efforts have to be focused on explicitly bridging VPH resources with clinical ontology frameworks. To this end, the VPH should encourage commercial providers of clinical terminology services to further simplify and actively support the mapping between biomedical terms they create and anatomical ontologies in the public domain.

## Conclusion

The VPH project works to advance the systematic integration of human reference data and resultant models across different scales and biomedical disciplines. The initial focus on the structural framework for such integration should ensure a fundamental degree of interoperability among VPH resources.

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## REFERENCES

1. Burger, A., et al., *Integrating partonomic hierarchies in anatomy ontologies*. BMC Bioinformatics, 2004. **5**: p. 184.
2. Smith, B., et al., *The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration*. Nat Biotechnol, 2007. **25**(11): p. 1251-5.
3. Degtyarenko, K., et al., *ChEBI: a database and ontology for chemical entities of biological interest*. Nucleic Acids Res, 2008. **36**(Database issue): p. D344-50.
4. Harris, M.A., et al., *The Gene Ontology (GO) database and informatics resource*. Nucleic Acids Res, 2004. **32**(Database issue): p. D258-61.
5. Bard, J., S.Y. Rhee, and M. Ashburner, *An ontology for cell types*. Genome Biol, 2005. **6**(2): p. R21.
6. Baldock, R.A., et al., *EMAP and EMAGE: a framework for understanding spatially organized data*. Neuroinformatics, 2003. **1**(4): p. 309-25.
7. Rosse, C. and J.L.V. Mejino, *The Foundational Model of Anatomy Ontology*, in *Anatomy Ontologies for Bioinformatics: Principles and Practice*, A. Burger, D. Davidson, and R. Baldock, Editors. 2007, Springer. p. 59-117.
8. Ordas, S., et al., *Computational Anatomy Atlas of the Heart*. 5th International Symposium on Image and Signal Processing and Analysis, 2007. ISPA 2007., 2007: p. 338-342.
9. Prlic, A., T.A. Down, and T.J. Hubbard, *Adding some SPICE to DAS*. Bioinformatics, 2005. **21 Suppl 2**: p. ii40-1.
10. Macias, J.R., N. Jimenez-Lozano, and J.M. Carazo, *Integrating electron microscopy information into existing Distributed Annotation Systems*. J Struct Biol, 2007. **158**(2): p. 205-13.
11. Venkataraman, S., et al., *EMAGE--Edinburgh Mouse Atlas of Gene Expression: 2008 update*. Nucleic Acids Res, 2008. **36**(Database issue): p. D860-5.
12. Jenkinson, A.M., et al., *Integrating biological data - the Distributed Annotation System*. BMC Bioinformatics, 2008. **9 Suppl 8**: p. S3.
13. Schulz, S., et al., *The semantics of procedures and diseases in SNOMED CT*. Methods Inf Med, 2006. **45**(4): p. 354-8.
14. Rubin, D.L., *Creating and Curating a Terminology for Radiology: Ontology Modeling and Analysis*. J Digit Imaging, 2007.