

# A Knowledge Representation View on Biomedical Structure and Function

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## Abstract

*In biomedical ontologies, structural and functional considerations are of outstanding importance, and concepts which belong to these two categories are highly interdependent. At the representational level both axes must be clearly kept separate in order to support disciplined ontology engineering. Furthermore, the biaxial organization of physical structure (both by a taxonomic and paratonic order) entails intricate patterns of inference. We here propose a layered encoding of taxonomic, paratonic and functional aspects of biomedical concepts using description logics.*

## INTRODUCTION

Many conceptualization efforts in the biomedical domain coincide in an upper-level distinction between tangible objects of the physical world, which are characterized by a spatial extension, on the one hand, and defined (changes of) states of the physical world, on the other hand.<sup>1</sup> Although these two subdomains are tightly related, their reasoning patterns are by no means straightforward. For example, the secretion of insulin is usually considered as a function of the pancreas, because the pancreatic beta cells are part of it. In the same way, muscular movement would be classified as a function of the muscle, since it is a function of the actin-myosin complex which is a component of muscle cells, the latter being part of the muscle. Such inferences – *function* propagates from physical parts to wholes – seem plausible. However, there are obvious counterexamples: Mitosis is a cell function, but certainly not a pancreas or liver function although these organs have cells as parts.

In this paper, we will discuss and classify typical reasoning patterns from which we derive our requirements for adequate domain modeling. Our focus will be on *Biological Function*, as a specialization of *Event*, and its interaction with *Biological Structure*. Both are

<sup>1</sup>The UMLS [14] distinguishes between *Entities* and *Events*, the GALEN ontology [6] between *GeneralizedStructure* and *GeneralizedProcess*, the Gene Ontology [4] between *Cellular Component* and *Biological Process*, and in the TAMBIS Ontology [2] this distinction is reflected by *GeneralizedStructure/GeneralizedSubstance* vs. *GeneralizedProcess/GeneralizedFunction*.

of paramount importance for the fields of anatomy, physiology, pathology as well as for cell and molecular biology. We then propose a suitable ontology engineering approach, based on our previous work on biomedical knowledge representation [13, 11, 12].

## STRUCTURE AND FUNCTION

In knowledge representation, concepts are characterized by their attributes, also called *slots* in frame-based representations or *roles* in description logic systems (e.g., *has-location*, *part-of*, ...), while role filler restrictions constrain their sortal ranges. *Liver*, e.g., is a reasonable filler of the role *has-location* of *Hepatitis*. With *C* being a concept, *r* one of its roles filled by the role filler *F*, we make the following distinctions:

- **Forbidden roles.** *F* is disallowed to be a filler of the role *r* at the concept *C*. As an example, for *C* = *Dermatitis* and *r* = *has-location*, a filler such as *F* = *Liver* must be rejected.
- **Optional roles.** Those roles of a concept *C* which can be filled but need not. As an example, the role *has-part.Nucleus* is an optional one when we define the concept *Cell*, since cells with and without nuclei exist (e.g. red blood cells).
- **Mandatory roles.** Those roles of a concept *C* which are required to be filled as, e.g., in the case of *has-location.Liver* in the above definition of *Hepatitis*. This allows to infer that for each concrete hepatitis there must be a concrete liver it affects.

In the following, we will focus on the distinction between *optional* and *mandatory* roles in the definition of *Structure* and *Function* concepts. We introduce the relations *part-of* and its converse *has-part* (abbreviated as *p* and *i* (*i* for “includes as part”)), which hold between *Structure* and *Structure*. Accordingly, we introduce *has-function* and *function-of* (abbreviated as *hf* and *fo*) which relate *Structure* and *Function*. Given these distinctions, when we analyze our domain the following observations can be made:

- In **Structure** concept definitions, roles filled by *Function* concepts mostly have the ‘optional’ status, since most functions in living systems can cease without any implications for the identity of the objects concerned. A *Liver Cell*, e.g., has normally

the function of *Lipid Biosynthesis*, but this is not a necessary condition, since even dead *Liver Cells* are still liver cells.<sup>2</sup>

- In **Function** concept definitions most roles are mandatory. The instantiation of *Insulin Biosynthesis*, e.g., requires the role *function-of* to be filled by one or more *Structure* concepts, e.g., *Beta Cells*.

As an intermediate representation we now specialize the relations *hf* and *fo* to distinguish between mandatory and optional functions such as given in Table 1:

Relation Name	Abbr.	Domain	Range
mandatorily-performed-by	<i>mpb</i>	Function	Structure
optionally-performed-by	<i>opb</i>	Function	Structure
has-mandatory-function	<i>hmf</i>	Structure	Function
has-optional-function	<i>hof</i>	Structure	Function

Table 1: Specialized relations between *Function* and *Structure*. The upper two relations are subrelations of *function-of* (*fo*), the lower ones are subrelations of *has-function* (*hf*). *Domain* characterizes the concept to be defined, *Range* the conceptual constraint on the role filler.

The distinction between optional and mandatory roles is equally important when we limit our view to *Structure* concepts and the mereological relations *part-of* and *has-part*. Such *partonomies* play a prominent role in biomedical ontologies (e.g., the Gene Ontology [4] and the Digital Anatomist Foundational Model [9]), and various researchers have already investigated their semantic foundations [1, 13, 8]. We subscribe to a non-constrained understanding of parthood in which the relations *p* and *i* are considered as reflexive, antisymmetric and transitive [3].

In a strict sense, mereological relations can only hold between individuals, not between concepts. It is obvious that for each pair of individuals ( $I_1, I_2$ ), related by *p*, the inverse relation *i* (has-part) always turns out to be true between ( $I_2, I_1$ ). The transfer of this symmetry to the level of concept definitions (as in the UMLS metathesaurus where there is exactly one *part-of* link for each *has-part* link) can only be justified under the assumption of all roles being optional. This constraint is, however, too weak for many purposes. So we distinguish between *optional* and *mandatory* parts and wholes. Hence, symmetry between *part-of* and *has-part* is no longer justified, taking common conceptualizations of the domain into account:

- (i) Every *Cell* has *Protein* as part, but not every *Protein* is part of a *Cell*.
- (ii) Every *Cell Nucleus* is part of a *Cell*, but not every *Cell* has a *Cell Nucleus*.

<sup>2</sup>Mandatory roles filled by *Function* concepts occur occasionally when a new concept is defined and the mandatory function role is taken as a definitional criterion. As an example, the concept *ReplicatingDNA* is defined as a *DNA* as long as the function *Replication* is performed.

Just as with the relations *fo* and *hf*, we resort to specialized partitive relation predicates as introduced in Table 2 and may assert:

- (i') *Cell hmp Protein*, but *Protein how Cell*,
- (ii') *Cell hop Cell Nucleus*, but *Cell Nucleus hmw Cell*.

Relation Name	Abbr.	Domain	Range
has-mandatory-part	<i>hmp</i>	Structure	Structure
has-optional-part	<i>hop</i>	Structure	Structure
has-mandatory-whole	<i>hmw</i>	Structure	Structure
has-optional-whole	<i>how</i>	Structure	Structure

Table 2: Relations between *Structure* and *Structure*. *hmp* and *hop* are subrelations of *has-part* (*i*), *hmw* and *how* of *part-of* (*p*).

We now analyze interactions between *Structure* and *Function* for plausible inferences. All possible combinations are listed in Table 3.

$\circ$	$WhmpP \wedge P hmw W$	$WhmpP \wedge PhowW$	$WhopP \wedge PhmwW$	$WhopP \wedge PhowW$
$F mpb W$	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
$F mpb P$	$F mpb W$	$F opb W$	$F mpb W$	$F opb W$
$F opb W$	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
$F opb P$	$F opb W$	$F opb W$	$F opb W$	$F opb W$
$W hmf F$	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
$P hmf F$	$W hmf F$	$W hof F$	$W hof F$	$W hof F$
$W hof F$	$\emptyset$	$\emptyset$	$\emptyset$	$\emptyset$
$P hof F$	$W hof F$	$W hof F$	$W hof F$	$W hof F$

Table 3: Composition table of plausible relation chains, involving relations between *Structure* Concepts (W = wholes, P = parts) and *Function* Concepts (F)

We now illustrate the reasoning patterns which derive from Table 3:

- *Insulin synthesis* is mandatorily performed by (*mpb*) the pancreatic *Beta Cells*. *Beta Cells* have *Islets of Langerhans* as a mandatory whole (*hmw*). We infer that *Insulin Synthesis* is also mandatorily performed by (*mpb*) *Islets of Langerhans*:

<i>Insulin Synthesis</i>	<i>mpb</i>	<i>Beta Cells</i>
<i>Beta Cells</i>	<i>hmw</i>	<i>Islets of Langerhans</i>
<i>Insulin Synthesis</i>	<i>mpb</i>	<i>Islets of Langerhans</i>

- The structure concept *Beta Cells* has the optional function (*hof*) *Insulin Synthesis* (it is not mandatory as it may be inactive in certain states). *Islets of Langerhans* have *Beta Cells* as an optional part (in case of certain types of diabetes these islets are devoid of beta cells). We infer that *Islets of Langerhans*, too, have *Insulin Synthesis* as an optional function:

<i>Beta Cells</i>	<i>hof</i>	<i>Insulin Synthesis</i>
<i>Beta Cells</i>	<i>hmw</i>	<i>Islets of Langerhans</i>
<i>Islets of Langerhans</i>	<i>hof</i>	<i>Insulin Synthesis</i>

- The inferences given in Table 3 can however not be taken for granted such as this atypical example illustrates:

Mitosis	<i>mpb</i>	Eukaryotic Cells
Human Body	<i>hmp</i>	Eukaryotic Cells
Mitosis	<i>mpb</i>	Human Body ???

This is a questionable inference, at least. There is also a subtle difference between a function *performed by* and a function *performed at*. For the latter we observe fewer exceptions.

As a result, we stipulate that a model capable of dealing with the standard inference patterns given in Table 3 should also be flexible enough to comply with exceptions to these patterns. Such an approach should overcome the limits of the *Grail* concept representation language [5], which although it provides means for dealing with the role propagation across part-whole hierarchies, has turned out to be too rigid to account for reasoning anomalies[7] such as discussed above.

### A DESCRIPTION LOGICS APPROACH

The problems stated in the previous section are addressed by the PI-model (from “part” / “include”) which extends our previous work on the *SEP* [13] and *Extended SEP* [11] models. Our approach, which has already proved valid for the integration of partonomic and taxonomic reasoning, is based upon a set-theoretic semantics underlying the description logics language  $\mathcal{ALC}$ [10]<sup>3</sup>.

The PI-model is centered around the relations  $p$  and  $i$  with the semantics introduced above. We emulate transitive mereological reasoning by taxonomic reasoning by introducing additional concepts which are introduced as ‘reificators’ of the relations  $p$  and  $i$ . For each *structure* concept ( $S$  in this example) we introduce, for both the  $p$  and the  $i$  relation, two artificial concepts as common subsumers for all those concepts which must have, by definition, the role  $p$  filled by  $S$ , or the role  $i$  filled by  $S$ , respectively.

$$S_p \sqsubseteq \exists p.S \quad (1)$$

$$S_i \sqsubseteq \exists i.S \quad (2)$$

So,  $S_p$  subsumes all concepts that have  $S$  as a *mandatory whole*, and  $S_i$  subsumes the ones having  $S$  as a *mandatory part*. As an example, the concept *Hand<sub>p</sub>* subsumes both *Finger* and *Thumb*.

Cascading subsumption of concepts (in parallel with the corresponding ‘part’ node) by ‘part’ nodes of their mandatory wholes emulates transitivity of the  $p$  relation (see Fig. 1). The same applies to the emulation

<sup>3</sup> $\mathcal{ALC}$  allows for the construction of hierarchies of concepts and relations, where  $\sqsubseteq$  denotes subsumption and  $\doteq$  definitional equivalence. Existential ( $\exists$ ) and universal ( $\forall$ ) quantification, negation ( $\neg$ ), conjunction ( $\sqcap$ ) and disjunction ( $\sqcup$ ) are supported. Role fillers are linked to the relation name by a dot, e.g.,  $\exists r.C$ .

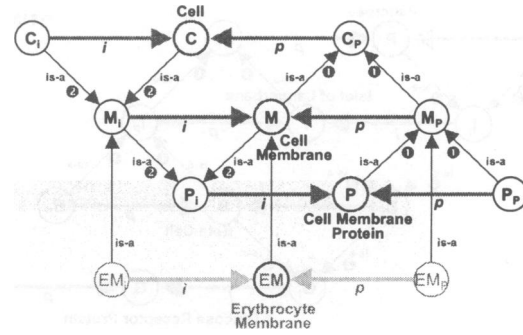


Figure 1: PI-Architecture: Emulation of transitivity of both  $p$  and its converse  $i$ . The *is-a* links with label (1) emulate part-of ( $p$ ) hierarchies, the *is-a* links with label (2) emulate has-part hierarchies ( $i$ ).

of  $i$  transitivity: In this case, concepts – together with their corresponding ‘include’ nodes – are subsumed by ‘include’ nodes of their mandatory parts.

Fig. 1 depicts a scenario in which mandatory parts correspond to mandatory wholes. Each instance of *Cell Membrane* ( $M$ ) has its role  $p$  filled by an instance of *Cell* ( $C$ ), because  $M$  is subsumed by  $C_p$ . Each *Cell* ( $C$ ) has the role  $i$  filled by an instance of *Cell Membrane*, because  $C$  is subsumed by  $M_1$  (the same applies to *Cell Membrane* ( $M$ ) and *Cell Membrane Protein* ( $P$ )). As  $P$  is subsumed by  $M_p$  and  $M_p$  by  $C_p$ , we infer that not only  $M$ , but also  $C$  is a mandatory whole for  $P$ . Accordingly,  $C$  is subsumed not only by  $M_1$ , but also by  $P_1$ , therefore both  $M$  and  $P$  are mandatory parts for  $C$  (in other words, each instance of *Cell* must have an instance of *Cell Membrane* and an instance of *Cell Membrane Protein* related by the relation *has-part*). In the lower plane of the figure an example for a subsumee of *Cell Membrane* (together with  $i$  and  $p$  node) is given in order to illustrate that the proposed encoding scheme is clearly distinct from a taxonomic order in an “orthogonal” way.

For a formal reconstruction of these considerations, let us assume  $C$ ,  $M$  and  $P$  to denote the concepts to be modeled, and  $C_p$ ,  $M_p$ , and  $P_p$  to denote “part” nodes, related to  $C$ ,  $M$ , and  $P$  via the role  $p$ . Accordingly  $C_i$ ,  $M_i$ , and  $P_i$  denote “include” nodes related to  $C$ ,  $M$ , and  $P$  via the role  $i$ :

$$M \sqsubseteq C_p \sqsubseteq \text{Structure} \quad (3)$$

$$M_p \sqsubseteq C_p \sqsubseteq \text{Structure} \quad (4)$$

$$P \sqsubseteq M_p \sqsubseteq C_p \sqsubseteq \text{Structure} \quad (5)$$

$$P_p \sqsubseteq M_p \sqsubseteq C_p \sqsubseteq \text{Structure} \quad (6)$$

$$M \sqsubseteq P_i \sqsubseteq \text{Structure} \quad (7)$$

$$M_i \sqsubseteq P_i \sqsubseteq \text{Structure} \quad (8)$$

$$C \sqsubseteq M_i \sqsubseteq P_i \sqsubseteq \text{Structure} \quad (9)$$

$$C_i \sqsubseteq M_i \sqsubseteq P_i \sqsubseteq \text{Structure} \quad (10)$$

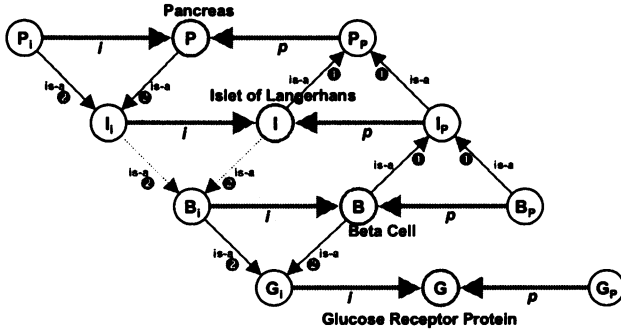


Figure 2: PI-Architecture: Asymmetric situation. Emulation of transitivity of both  $p$  and its converse  $i$ . The  $is-a$  links with label (1) emulate the part-of ( $p$ ) hierarchies, the  $is-a$  links with label (2) emulate the has-part hierarchies ( $i$ ). The dotted arrows have to be removed when the domain allows for pathological modifications concept *Pancreas* (which may be devoid of *Beta Cells* in certain types of diabetes).

$$C_P \sqsubseteq Structure \quad \sqcap \quad \exists p.C \quad (11)$$

$$M_P \sqsubseteq Structure \quad \sqcap \quad \exists p.M \quad (12)$$

$$P_P \sqsubseteq Structure \quad \sqcap \quad \exists p.P \quad (13)$$

$$C_I \sqsubseteq Structure \quad \sqcap \quad \exists i.C \quad (14)$$

$$M_I \sqsubseteq Structure \quad \sqcap \quad \exists i.M \quad (15)$$

$$P_I \sqsubseteq Structure \quad \sqcap \quad \exists i.P \quad (16)$$

It is obvious that, using this pattern across various physical concepts linked with each other via the  $p$  or the  $i$  relation, we get the same deductions as if  $p$  and  $i$  were really transitive at the level of concepts.

The flexibility of this approach is shown in Fig. 2. Here the (dotted)  $is-a$  links between  $I$  and  $B_I$ , and  $I_I$  and  $B_I$ , respectively, constrain the concept *Islets of Langerhans* in terms of disallowing pathologically modified instances (which have no *Beta Cells*) requiring *Beta Cells* as mandatory part. Another pair of links between *Glucose Receptor Protein* and *Beta Cell* is omitted intentionally, since the latter is not *mandatory* (glucose receptor proteins occur in many kinds of cells).

In the following we will discuss whether the proposed part-whole model is capable of accounting for the most common inferences given in Table 3. Note that the model itself does not use any of the specialized relations from Table 3.

For *Structure* concept definitions we raise the following claims:

- A *Structure* concept  $W$  has a mandatory part  $P$ .  $P$  has the optional function  $F$  (e.g.,  $W = Lung$ ,  $P = Alveolus$ ,  $F = Gas Exchange$ ). The rule to be applied here, is  $P \text{ hof } F \circ W \text{ hmp } P \rightarrow W \text{ hof } F$ . Since our language specification does not support the notion of optional roles proper (it allows only existential and universal quantification of roles), we have to introduce specialized roles, here for the function  $F$  the role  $hf-F \sqsubseteq hf$  which has its range restricted to  $F$ . This role is attached not only to  $P$ , but also to the

“include” node  $P_I$ . Thus the role is inherited to all subsumees of  $P_I$ , i.e. to  $P$  and all other concepts which have  $P$  as a mandatory part.

$$P_I \sqsubseteq \exists i.P \quad (17)$$

$$W_I \sqsubseteq \exists i.W \quad (18)$$

$$W \sqsubseteq P_I \quad (19)$$

$$W_I \sqsubseteq P_I \quad (20)$$

$$P \sqsubseteq \forall hf-F.F \quad (21)$$

$$P_I \sqsubseteq \forall hf-F.F \quad (22)$$

Wherever this behavior does not comply with shared inferential intuitions, expression (22) can be omitted. Otherwise, the function role is propagated through the ‘includes’ hierarchy, so we obtain the subsumptions:

$$W \sqsubseteq \forall hf-F.F \quad (23)$$

and so on for  $W_I$  and its subsumees.

- The following inference is not supported by our encoding:  $P \text{ hof } F \circ W \text{ hop } P \rightarrow W \text{ hof } F$  (e.g.,  $W = Pancreas$ ,  $P = Beta Cell$ ,  $F = Insulin Biosynthesis$ ), because of the already mentioned problem to express the notion of optional roles proper by our knowledge representation language.

For *Function* concept definitions we stipulate the following:

- A *Function* concept  $E$  is defined, being mandatorily functional for the *Structure* concept  $P$ .  $P$  has a mandatory whole  $W$ . We want to enforce inferences such as  $E \text{ mpb } P \circ P \text{ hmw } W \rightarrow E \text{ mpb } W$ . In case another *Function* concept  $F$  exists which is mandatorily functional for  $W \sqcup W_P$ , then  $F$  subsumes  $E$ , since  $P$  is subsumed by  $W_P$ :

$$P_P \sqsubseteq \exists p.P \quad (24)$$

$$W_P \sqsubseteq \exists p.W \quad (25)$$

$$P \sqsubseteq W_P \quad (26)$$

$$P_P \sqsubseteq W_P \quad (27)$$

Next, the functions are defined:

$$E \doteq Function \sqcap \exists fo.P \quad (28)$$

$$F \doteq Function \sqcap \exists fo.(W \sqcup W_P) \quad (29)$$

So we infer:

$$E \sqsubseteq F \quad (30)$$

because  $P$  is subsumed by  $W_P$  (e.g.,  $W = Kidney$ ,  $P = Glomerulum$ ,  $E = Glomerular Filtration$ ,  $F =$

*Renal Function*). This behavior can be obviated by restricting the range to  $W$  only (excluding  $W_P$ ):

$$F \doteq \text{Function} \sqcap \exists fo.W \quad (31)$$

- A *Function* concept  $F$  is defined, being mandatorily performed by the *Structure* concept  $P$ .  $P$  has a mandatory whole  $W$ . We want to allow inferences such as  $F \text{ mpb } P \circ W \text{ hmp } P \rightarrow F \text{ mpb } W$  (e.g., again  $W = \text{Lung}$ ,  $P = \text{Alveolus}$ ,  $F = \text{Gas Exchange}$ ).

$$P_I \sqsubseteq \exists i.P \quad (32)$$

$$W_I \sqsubseteq \exists i.W \quad (33)$$

$$W \sqsubseteq P_I \quad (34)$$

$$W_I \sqsubseteq P_I \quad (35)$$

In its definition  $F$  has the role  $fo$  filled by the disjunction of  $P$  and its I-node  $P_I$ :

$$D \doteq \text{Function} \sqcap \exists fo.(P \sqcup P_I) \quad (36)$$

Since  $P_I$  subsumes  $W$ , the latter is contained in the range of the  $fo$  role in the definition of  $F$ . Here too, an “exception handling” is possible by excluding  $P_I$  from the range of the function  $fo$  in expression (35) (e.g., with  $W = \text{Organism}$ ,  $P = \text{Eukaryotic Cell}$ ,  $F = \text{Mitosis}$ ).

- When defining functions related to *optional* wholes, the expected inferences would require additional nodes, as discussed above.

Summing up, the *PI* encoding provides not only an elegant way to simulate *part-of* and *has-part* transitivity by taxonomic subsumption, but also more flexibility in defining both *Function* concepts and *Function* roles in *Structure* concept definitions. By adding two “proto-nodes” for every *Structure* concept, several control mechanisms for the propagation of roles within mereological hierarchies exist which allow for a more precise adaptation of the ontology to common conceptualizations in the biomedical domain.

## CONCLUSIONS

The notions of biomedical structure and function not only require to sort out appropriate general ontological categories but also to take care of typical reasoning patterns. Our solution is based on a layered modeling strategy for concepts within standard description logics, essentially based upon the introduction of additional concepts as reificators for the relations *part-of* and *has-part*. These artifacts not only enable the propagation of roles across partonomic hierarchies, but also the accommodation of exceptions from standard reasoning patterns. There are other approaches to the handling of such exceptions, e.g., by specific subrelations

of mereological relations [8], but in any case the gain in flexibility has to be traded against the proliferation of (artificial) concepts and relation hierarchies. Due to the parsimony of the underlying language scalability is an asset, as we have demonstrated in a previous study in which a very large terminological knowledge base was constructed [12] using a similar approach.

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