Scalable representations of diseases in biomedical ontologies

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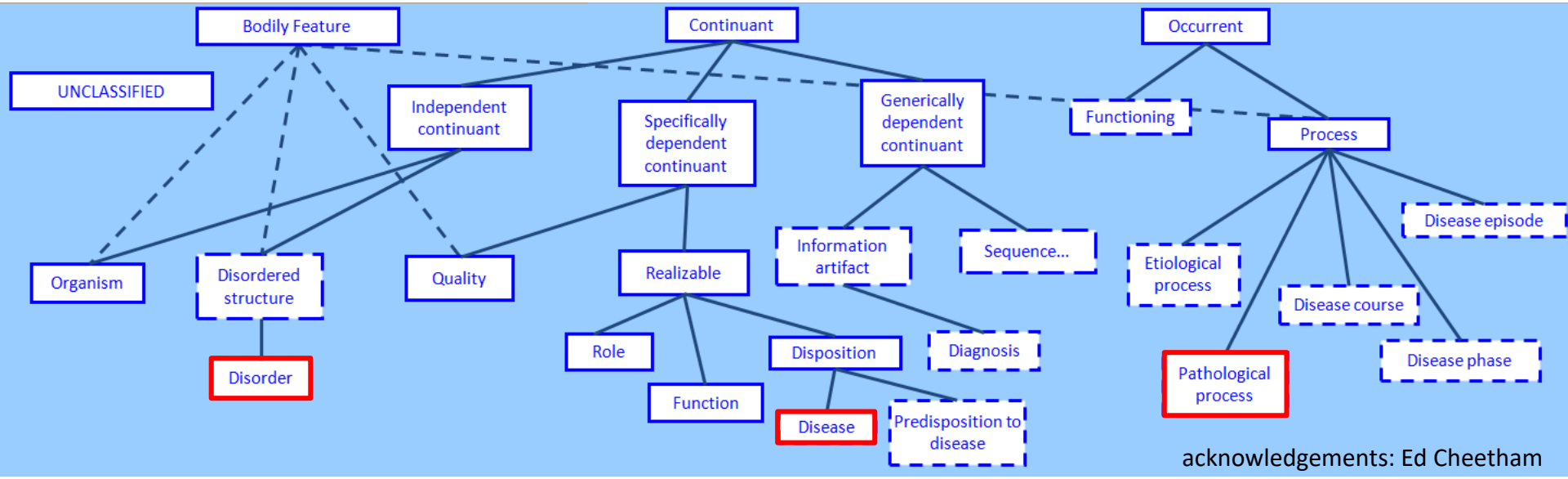
Ontological Nature of Disease

- Hucklenbroich 2007: diseases are processes, events, or states
- Williams 2007: diseases are dispositional entities
- Scheuermann, Smith 2009: diseases are dispositions, disorders are abnormal bodily components, and the manifestation of diseases are pathological processes
- SNOMED CT: Diseases under “Disorder”, “Finding”, “Event”, (rearrangement currently being discussed in the IHTSDO Event, condition, episode PG)

Diseases, disorders, pathological processes in disjoint BFO categories



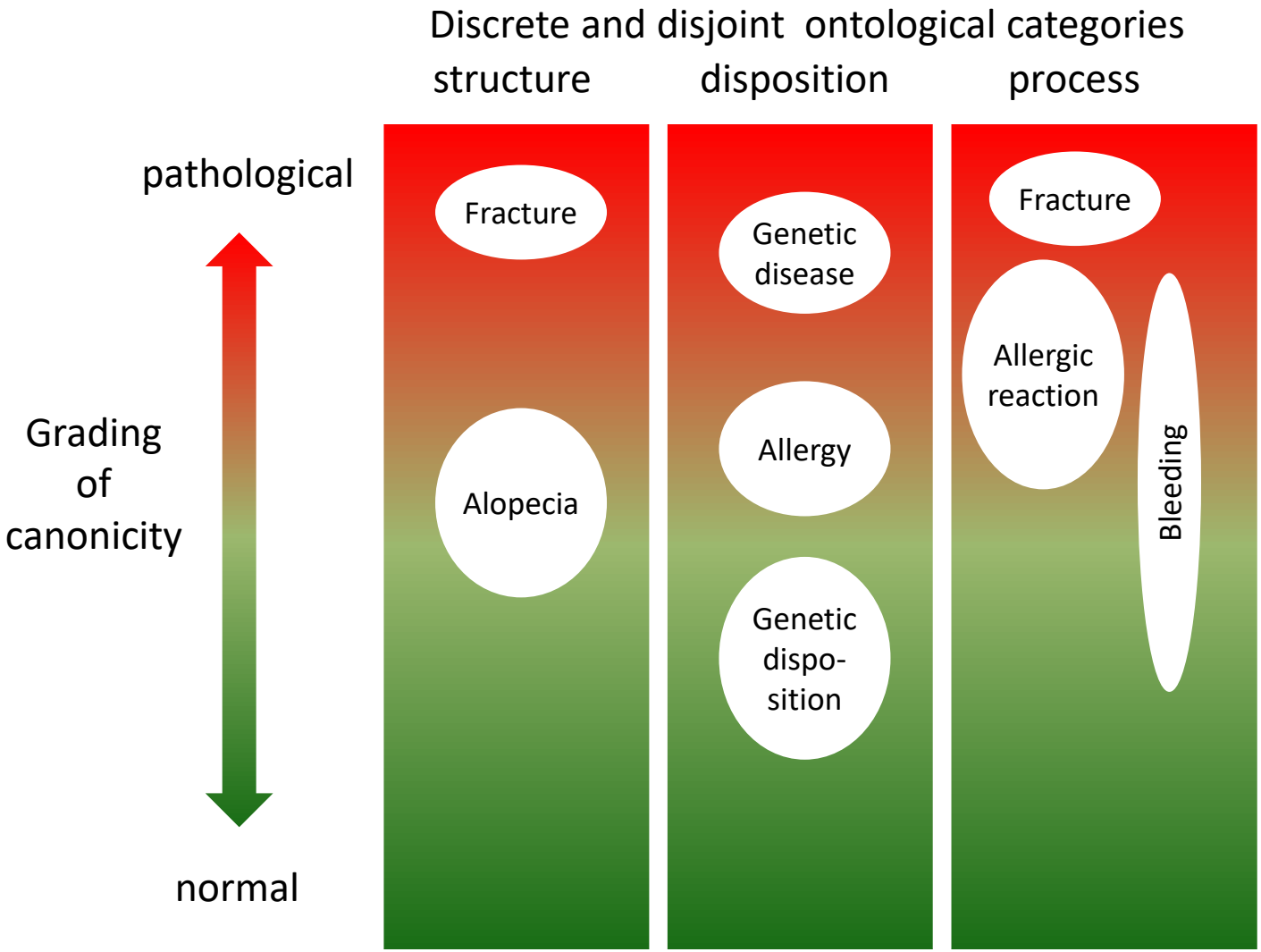
90310002	Deficiency of saccadic eye movements (disorder)
194175003	Abnormal optokinetic response (finding)
370948005	Anterior capsule opacification (finding)
410568009	Anterior capsule opacification (disorder)
425558002	Azoospermia (disorder)
48188009	Azoospermia (finding)
89684003	Bends (disorder)
282977007	Does bend (finding)
399221001	Bleeding from vagina (disorder)
289530006	Bleeding from vagina (finding)
417237009	Blister of skin AND/OR mucosa (finding)
247464001	Blistering eruption (disorder)

35489007	Depressive disorder (disorder)
41006004	Depression (finding)
246815009	Excess skin of eyelid (finding)
58588007	Cutis laxa (disorder)
25702006	Alcohol intoxication (disorder)
86933000	Heavy drinker (finding)
46690002	Disorder of skin pigmentation (disorder)
3253007	Discoloration of skin (finding)
229694001	Oral dyskinesia (disorder)
9748009	Dyskinesia (finding)
242784006	Exposure to electric current, with passage of current through tissue (event)

Two Major Problems

- Being pathological is rather a result of interpretation than a categorial property
  - Example: bleeding, pain, depression
- Ontologically motivated distinctions between disease, disorder, pathological process no not match the current meaning of words like “disease”, “disorder”, “abnormality” etc.

Disease matrix



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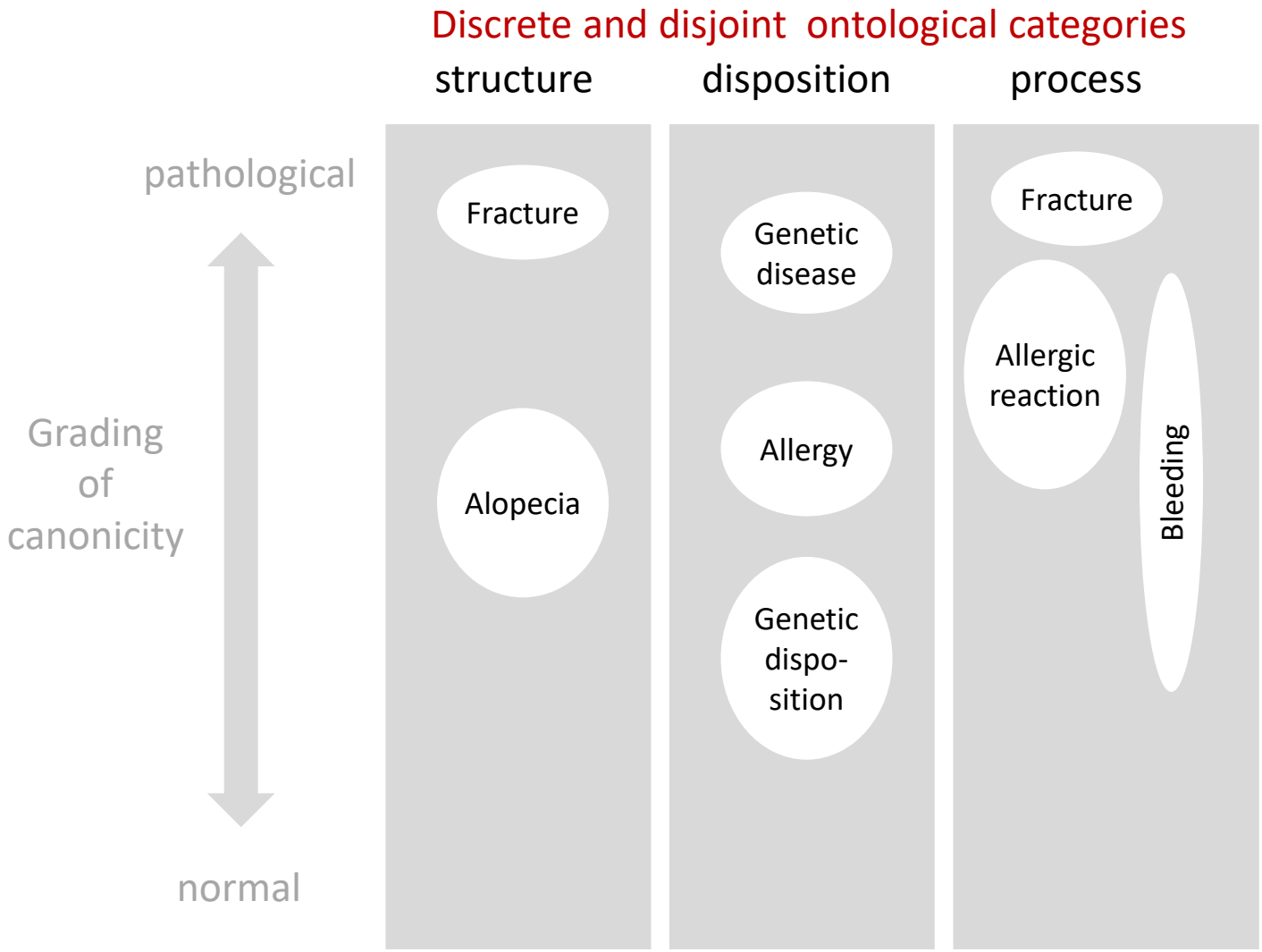


Redefinition: avoiding ambiguous terms like disease, disorder

- ~~Disorder~~ **Pathological Structure**: a combination of bodily components of or in an organism
  1. that is not part of the life plan for an organism of the relevant type (thus aging or pregnancy are not clinically abnormal),
  2. that is causally linked to an elevated risk of pain or other feelings of illness or of death or dysfunction on the part of the organism, and
  3. that it is such that this elevated risk exceeds a certain threshold level.
- ~~Disease~~ **Pathological Disposition**: disposition
  1. to undergo pathological processes that
  2. exists in an organism because of one or more pathological structures in that organism.
- **Pathological Process**: bodily process that is a manifestation of a pathological disposition.

according to Scheuermann & Smith, 2009

Formalization of Scheuermann & Smiths definitions

PathologicalDisposition ⊑

∃ **inheresIn** .*PathologicalStructure*

PathologicalProcess ⊑

∃ **hasParticipant** .*PathologicalStructure*

PathologicalProcess ⊑

∃ **realizationOf**. *PathologicalDisposition* ?

PathologicalDisposition ⊑

∀**hasRealization**. *PathologicalProcess*

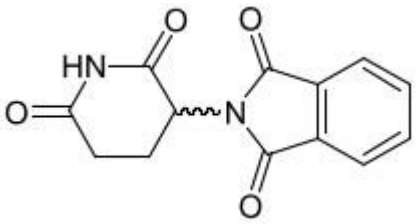
Example 1

- *Allergy* is a disposition of specific components of the immune system of an organism.
- All instances of the process type *Allergic Reaction*, are realizations of a disposition of this type, and have an allergen as their causative agent.

Image credit: http://www.topnews.in/health/files/Allergy.jpg

Example 2

- A specific binding of thalidomide to DNA forms a pathological structure on a molecular level
- This structure is the bearer of the pathological disposition realized by the misdevelopment of limbs (process) and results in a body without forearms (pathological structure)



Thalidomide

Image credit: http://www.mensch-home.com/Bilder/contergan-co-b/missbild-bild5g.jpg

Example 3

- The fracture (process) is caused by an external force, and has a fractured bone (pathological structure) as its characteristic outcome. This event is, however, not the realization of a disposition
- A fractured bone (structure) has many pathological dispositions which can result in a variety of pathological processes (e.g. the development of a pseudarthrosis).

Image credit:
http://www.bcyr.ca/Survivor/Fracture[1].jpg

Ontological soundness vs. engineering requirements

- Ontology engineering: labor-intensive, use case-driven
- Not realistic to implement this model
  - in each well-founded ontology from the very beginning
  - for all pathological entities to be represented
- Problem: how can a coarse-grained, pragmatic representation (which ignores the structure / disposition / process distinction) gracefully evolve towards a more sophisticated ontology?
- Can this be done in a intuitive, user-friendly, ontologically sound, computable, and scalable way?

Disjunctive class

- *PathologicalEntity* ≡

  PathologicalStructure ⊔

  PathologicalDisposition ⊔

  PathologicalProcess

- Top node of disease / disorder hierarchy (as long as no distinction made between processes, structures, dispositions)

Relation to organism parts / locations

… crucial for defining pathological entities

Different relations (e.g. OBO RO, BioTop)

- *Pathological Structures*: **part-of** / **located-in**
- *Pathological Dispositions*: **inheres- in**
- *Pathological Processes*: **has-participant**

  located-in

Redesign of relation hierarchy in the BioTop domain upper level ontology

… allows connection to organism parts or locations, without commitment to structure, disposition, or process

part-of $\sqsubseteq$ **has-locus**

has-location $\sqsubseteq$ **has-locus**

inheres-in $\sqsubseteq$ **has-locus**

has-participant $\sqsubseteq$ **locus-of**

locus-of $\equiv$ **has-locus**$^{-1}$ **:** reflexive and transitive relation

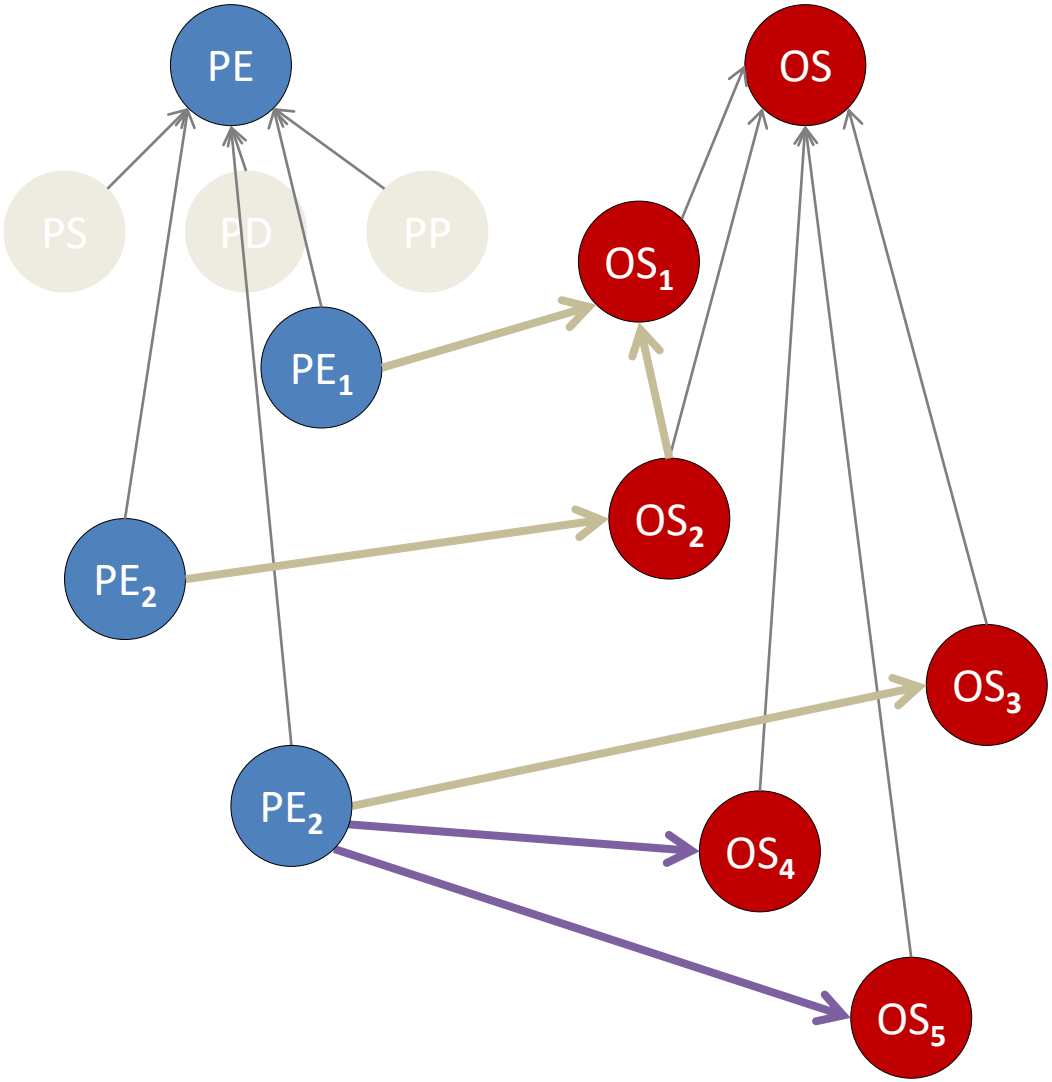
Corollaries of relation abstraction

- a disposition of a part is also borne by the whole
- a pathological structure located in a part is also located in the whole
- a process located in a part is also located in the whole
- all participants of a process are located where the process is located




Construction of basic disease ontology

- Basic components:
  - Top nodes
    - PE *Pathological Entity*
    - OS *Organism Structure*
  - Disease classes (broad sense)
  - Organism structure classes
  - transitive relations
    - ∃ **has-locus**
    - ∃ **locus-of**



Construction of advanced disease ontology

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- Advanced components

PS *PathologicalStructure*

PD *PathologicalDisposition*

PP *Pathological Process*

  - Relations
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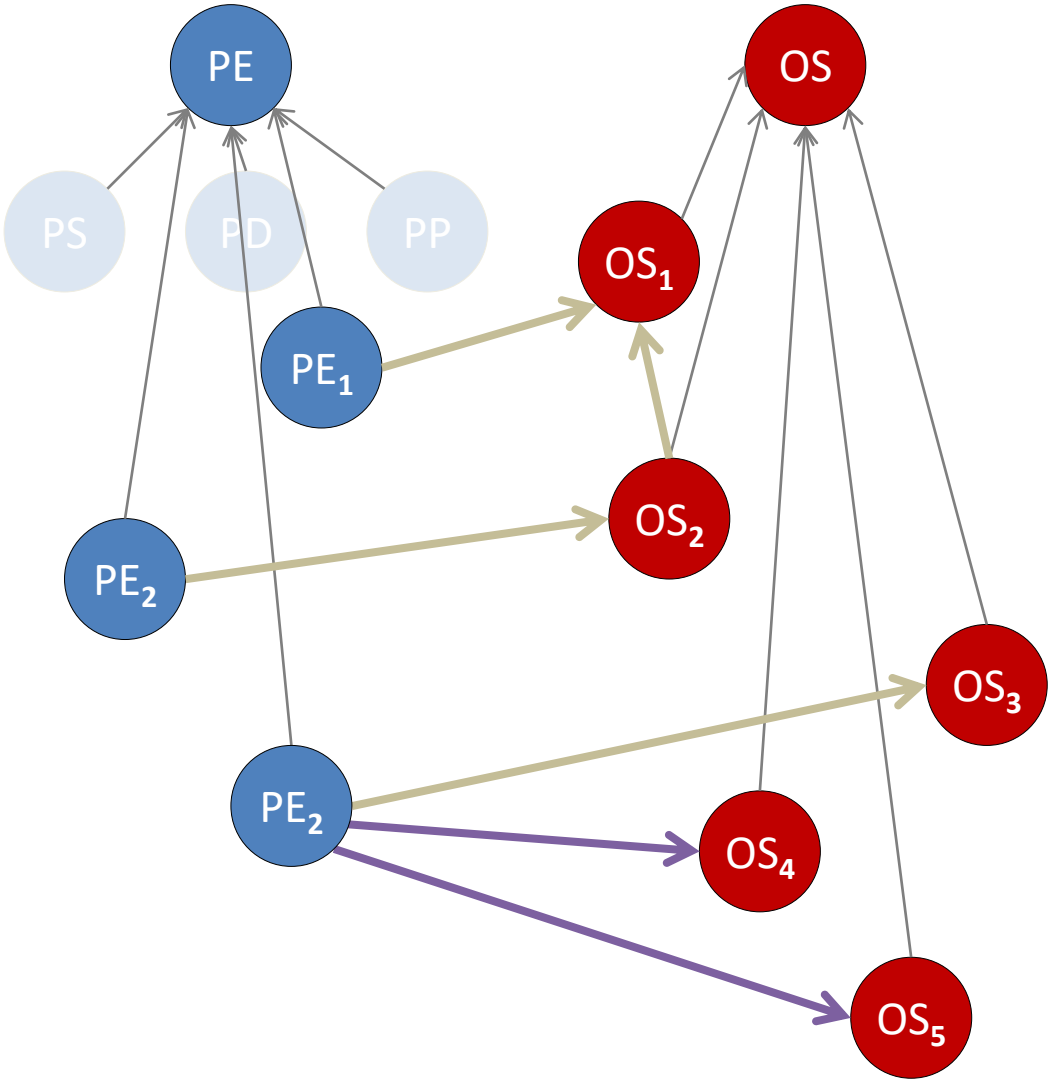
    - ∃ **has-location**
    - ∃ **has-participant**



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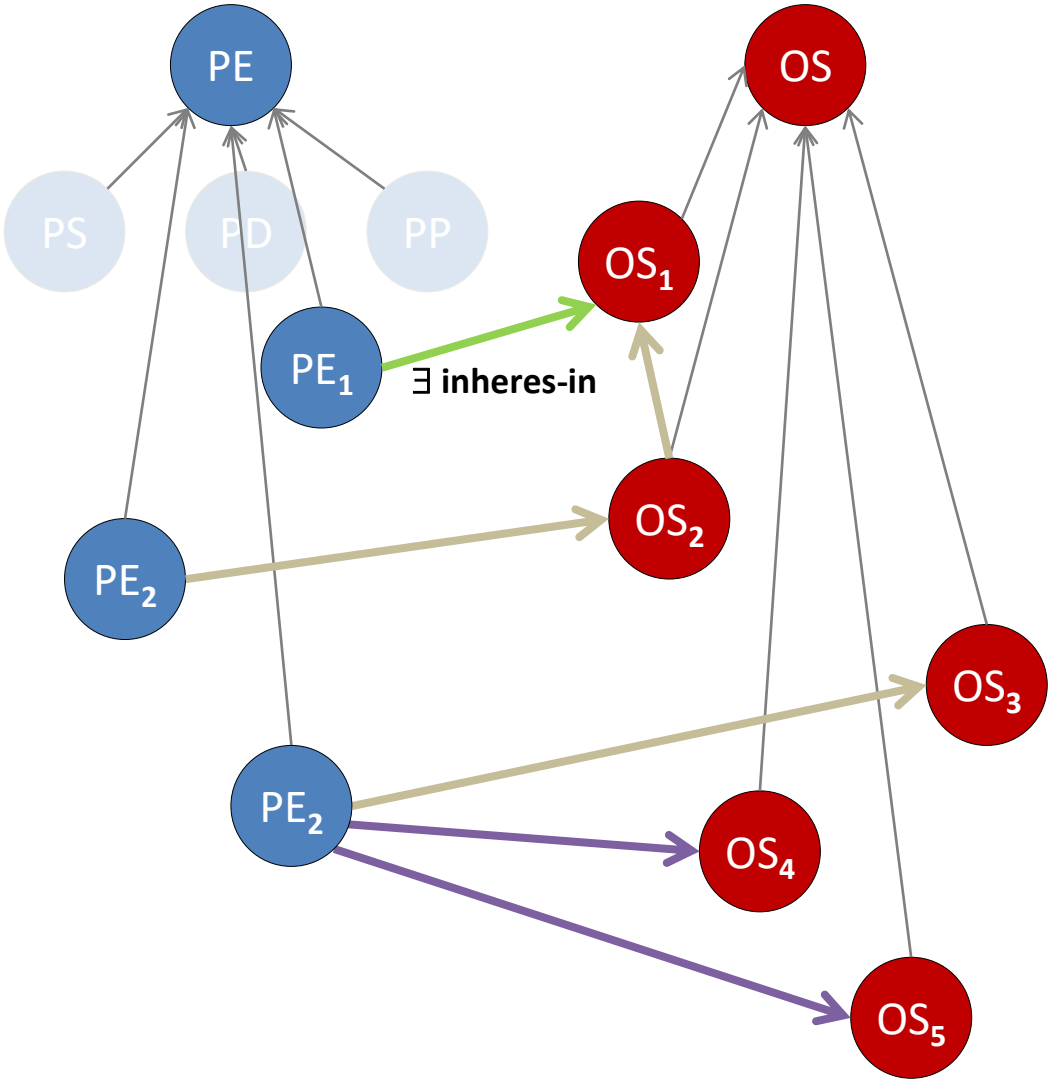

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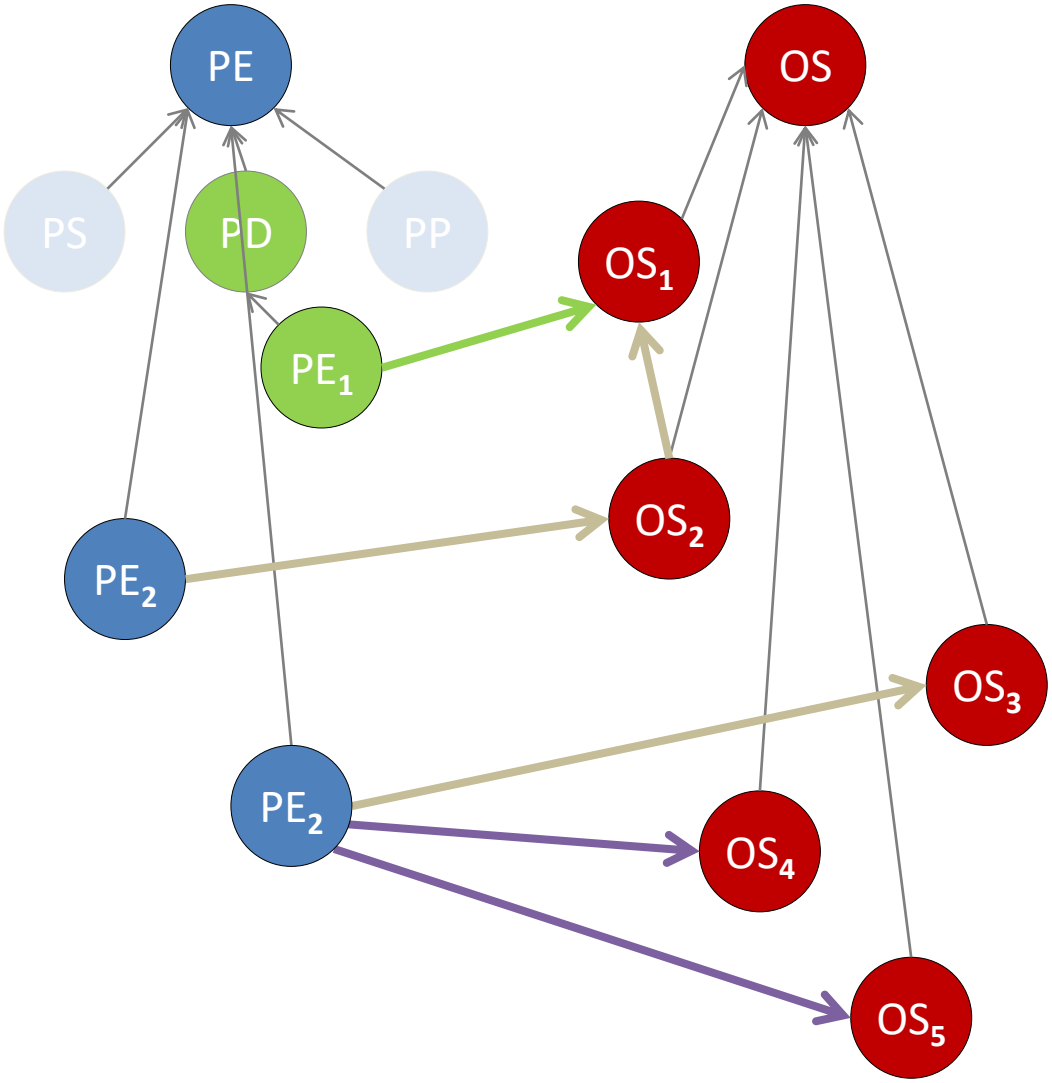

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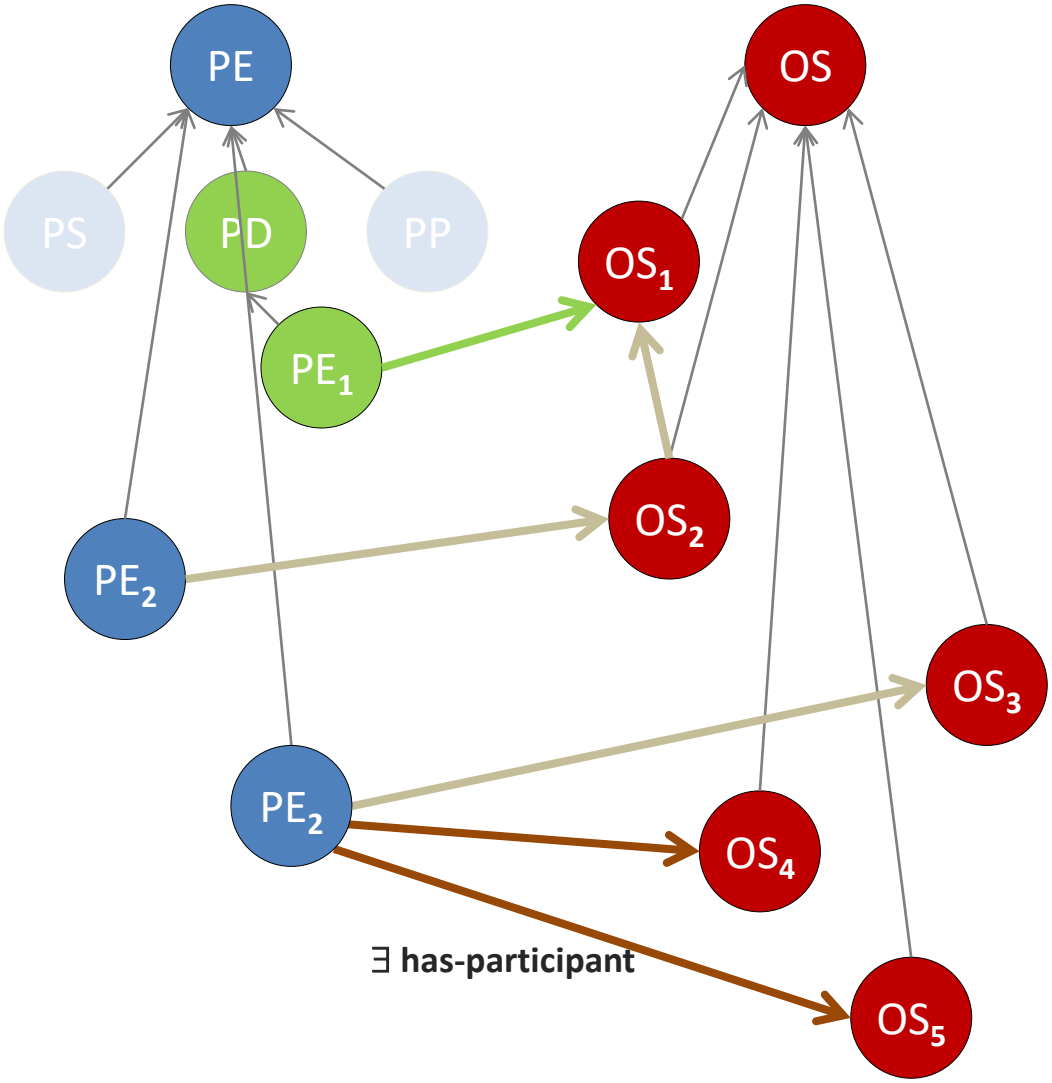

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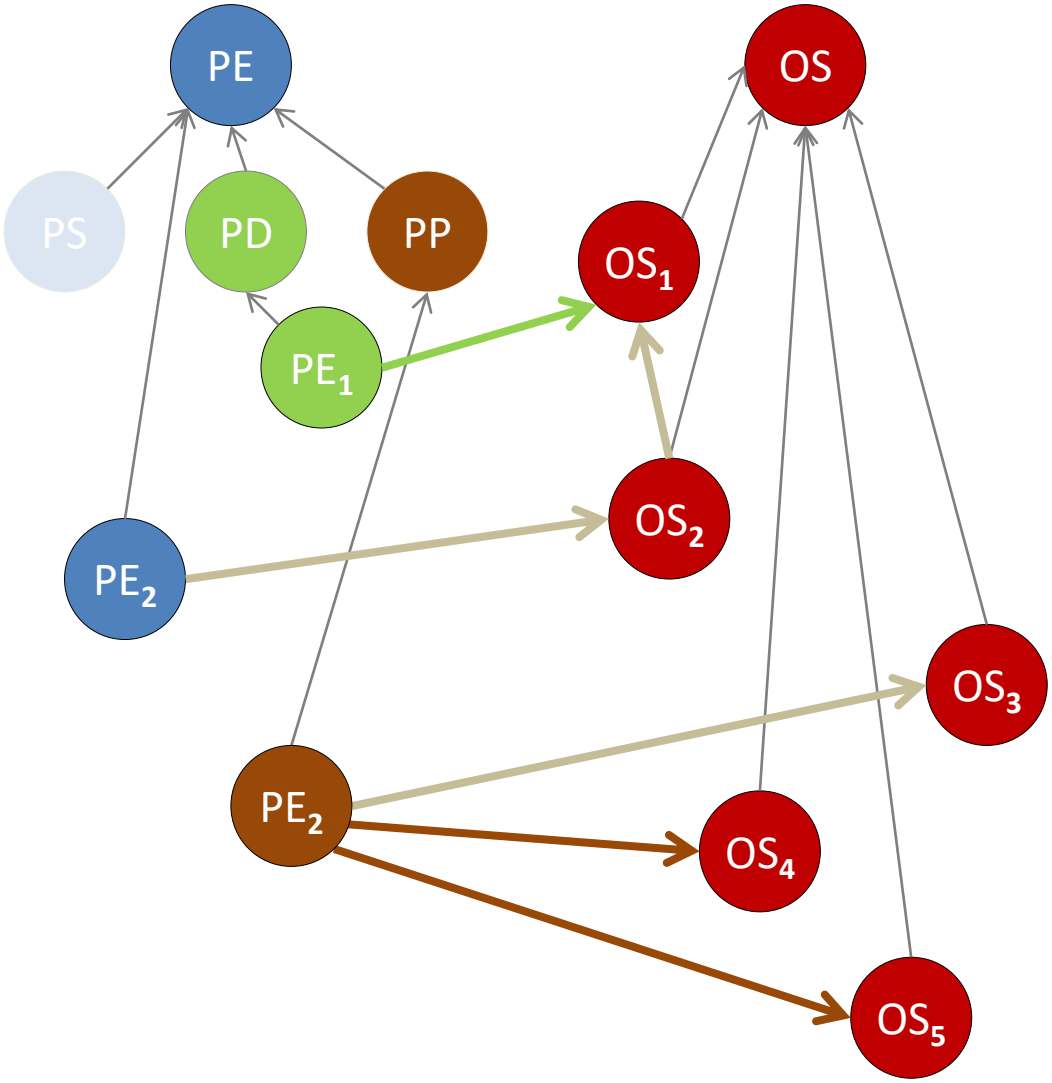

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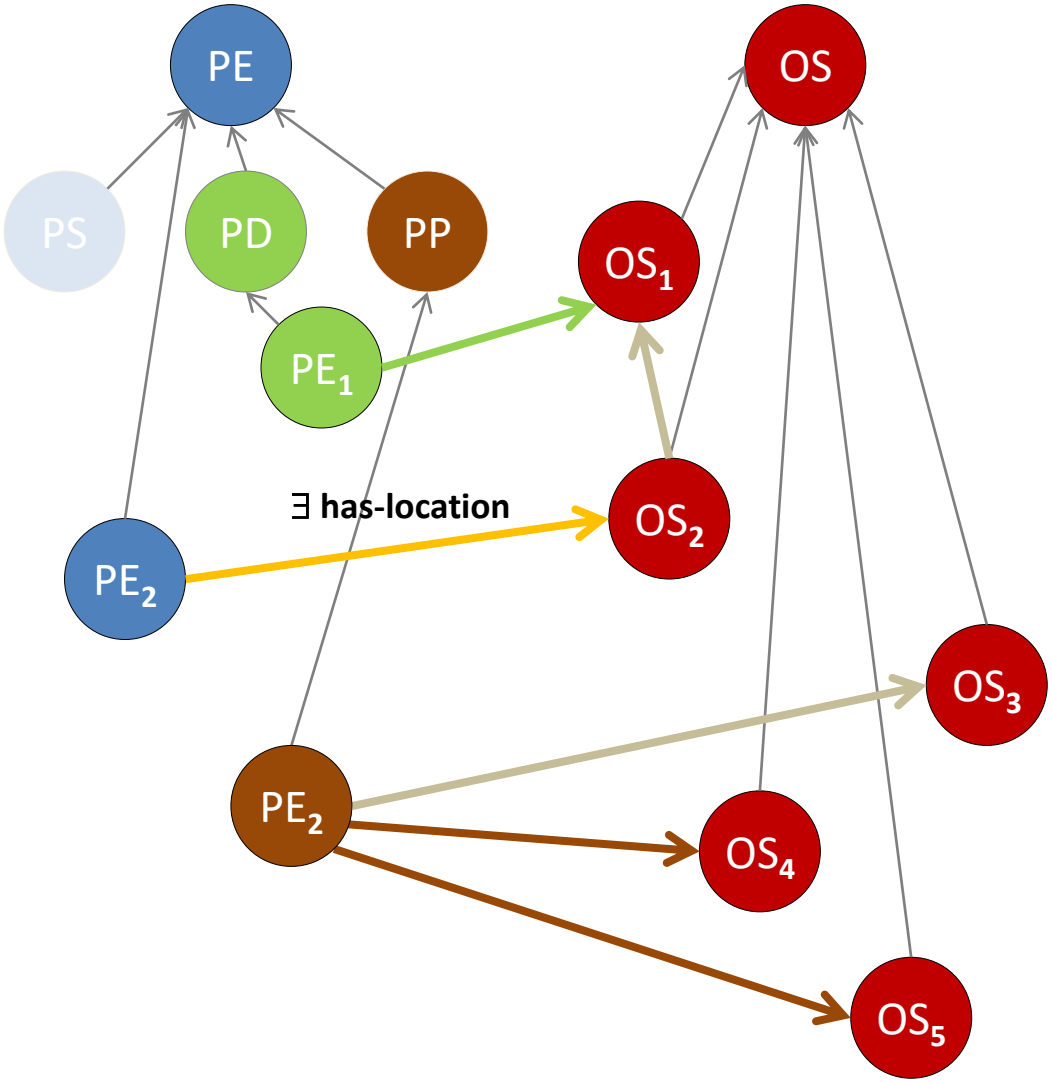

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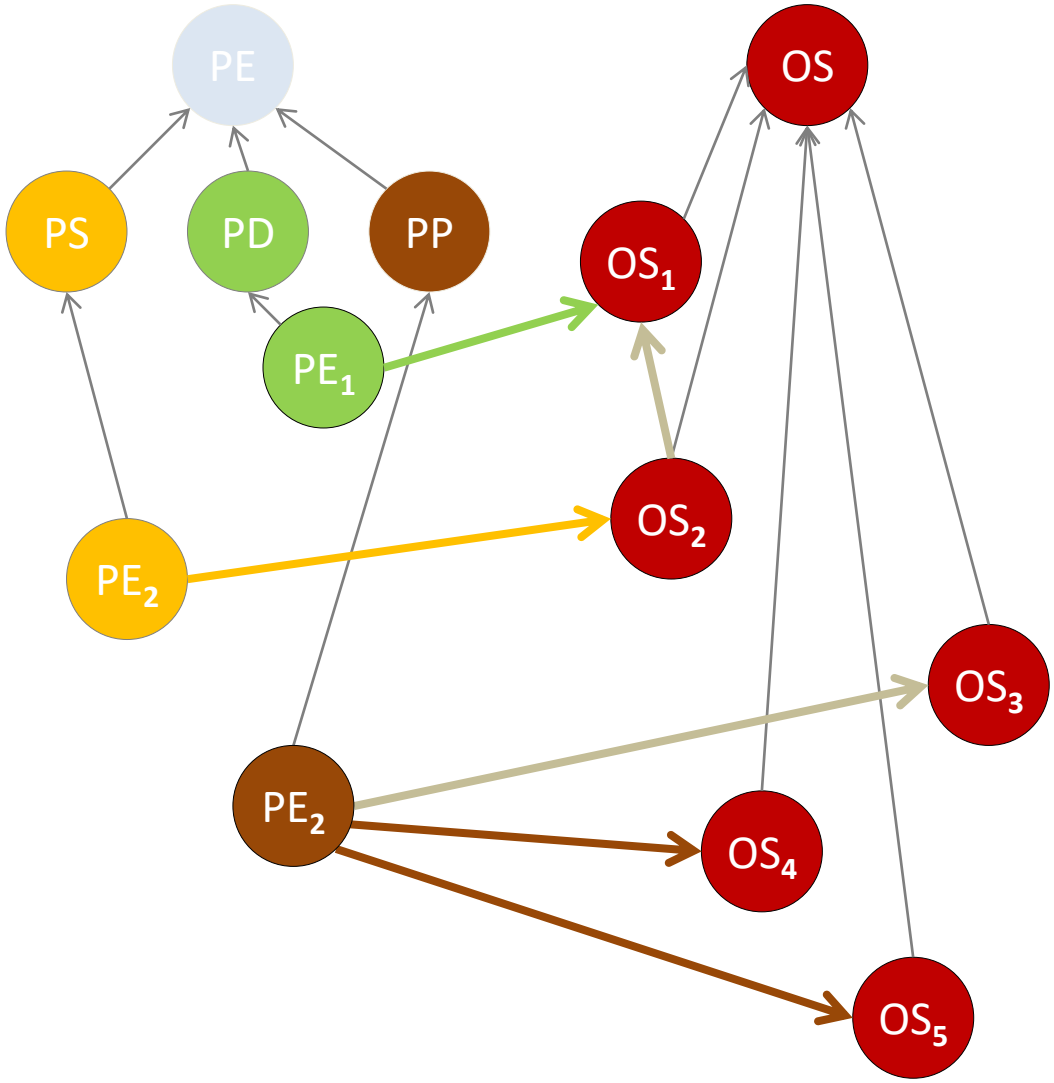

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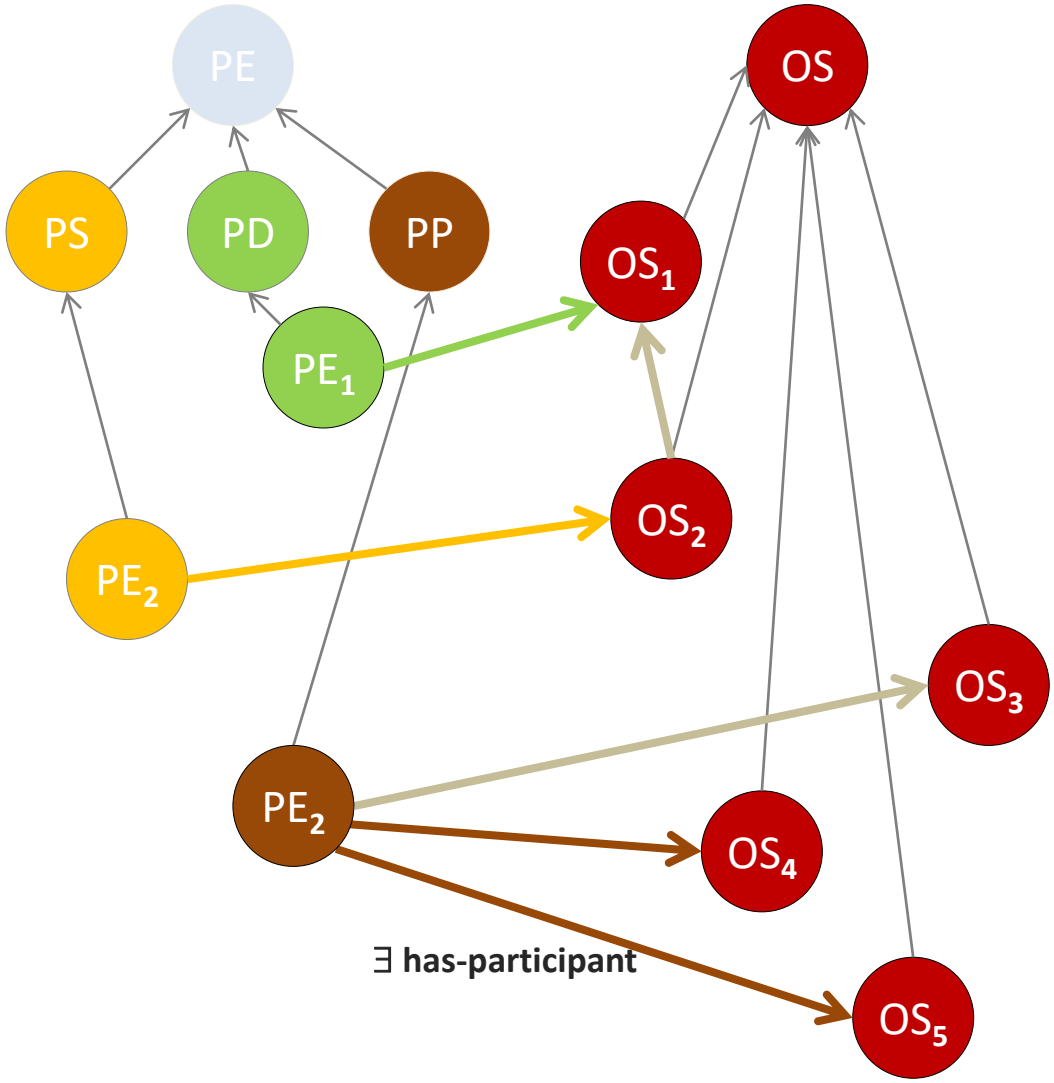

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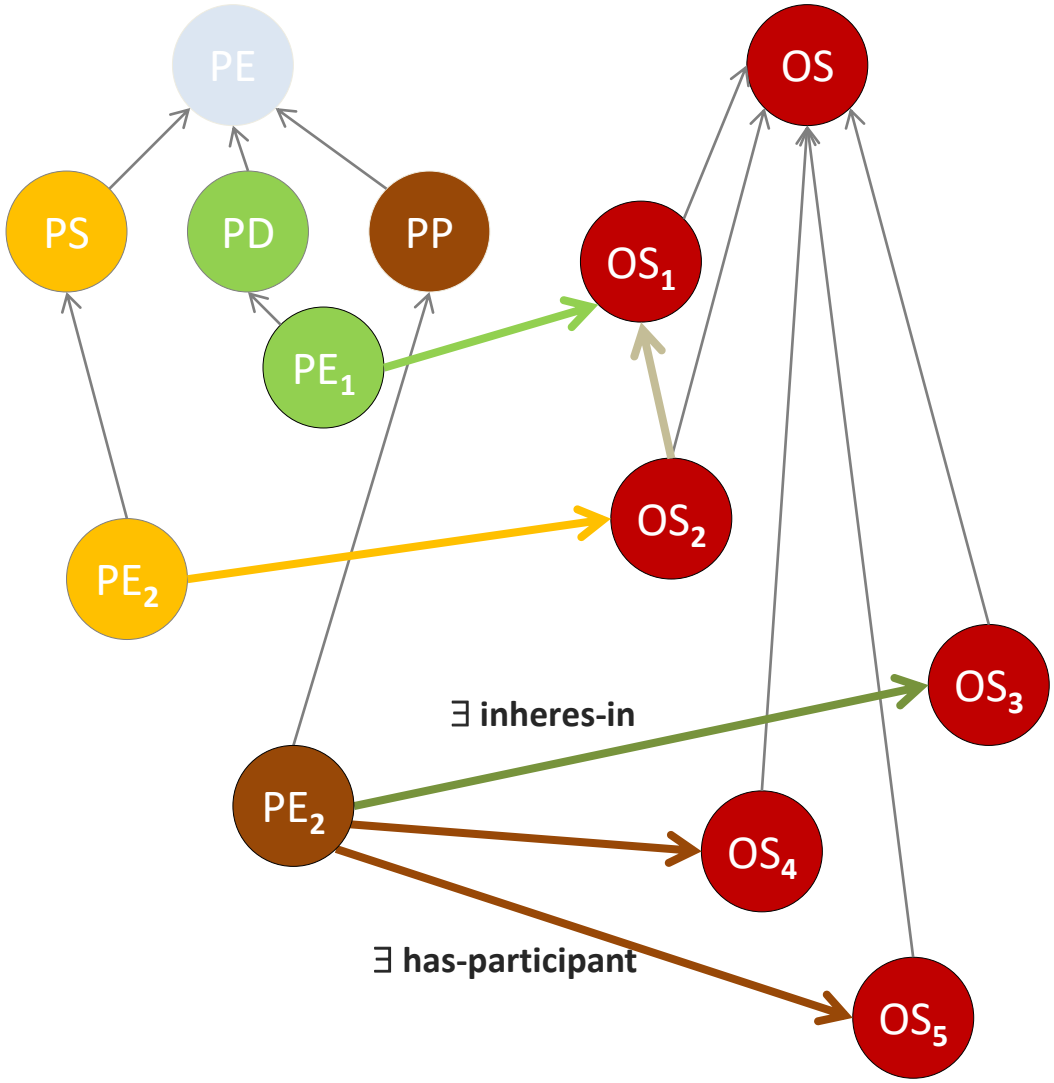

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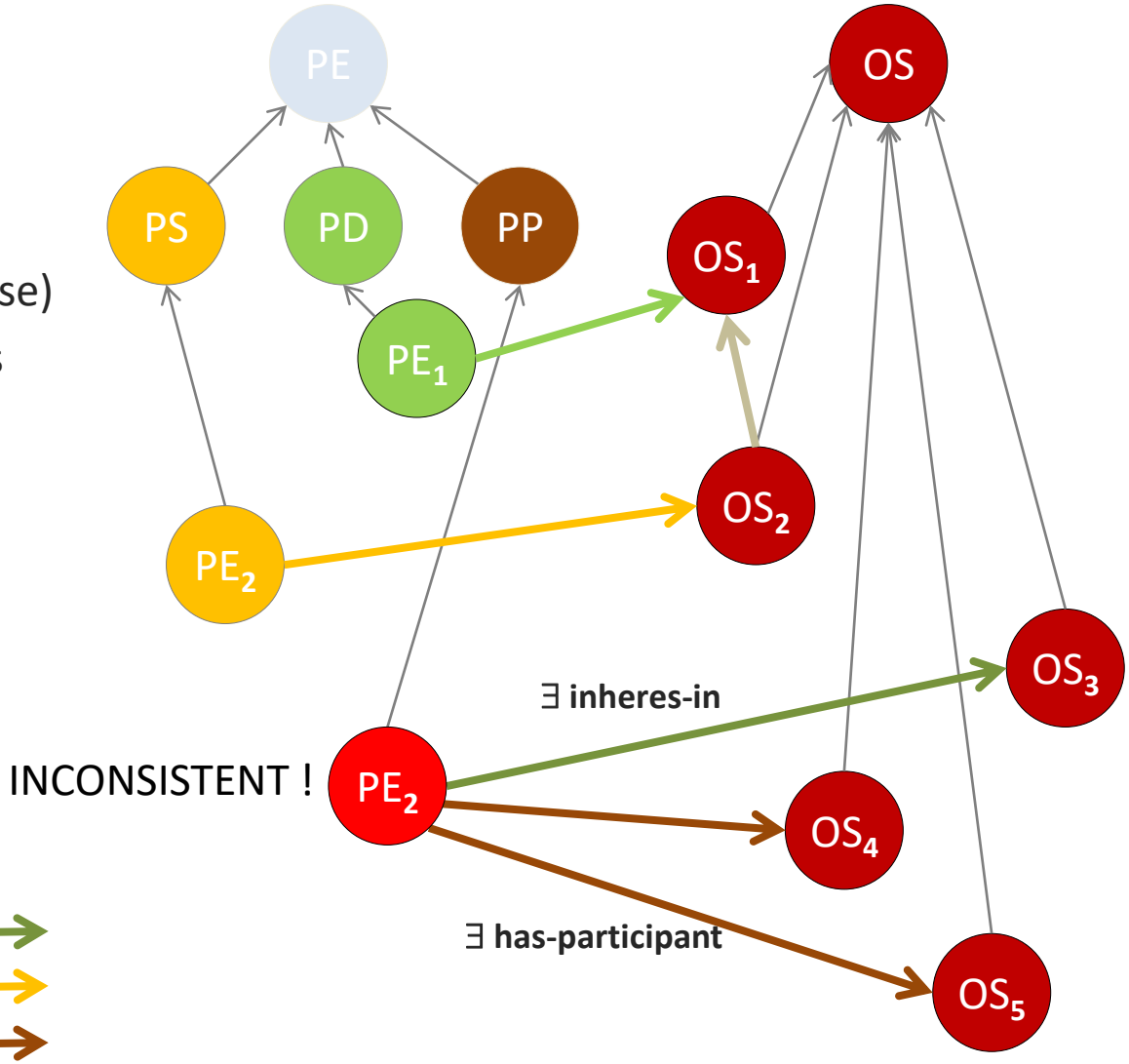

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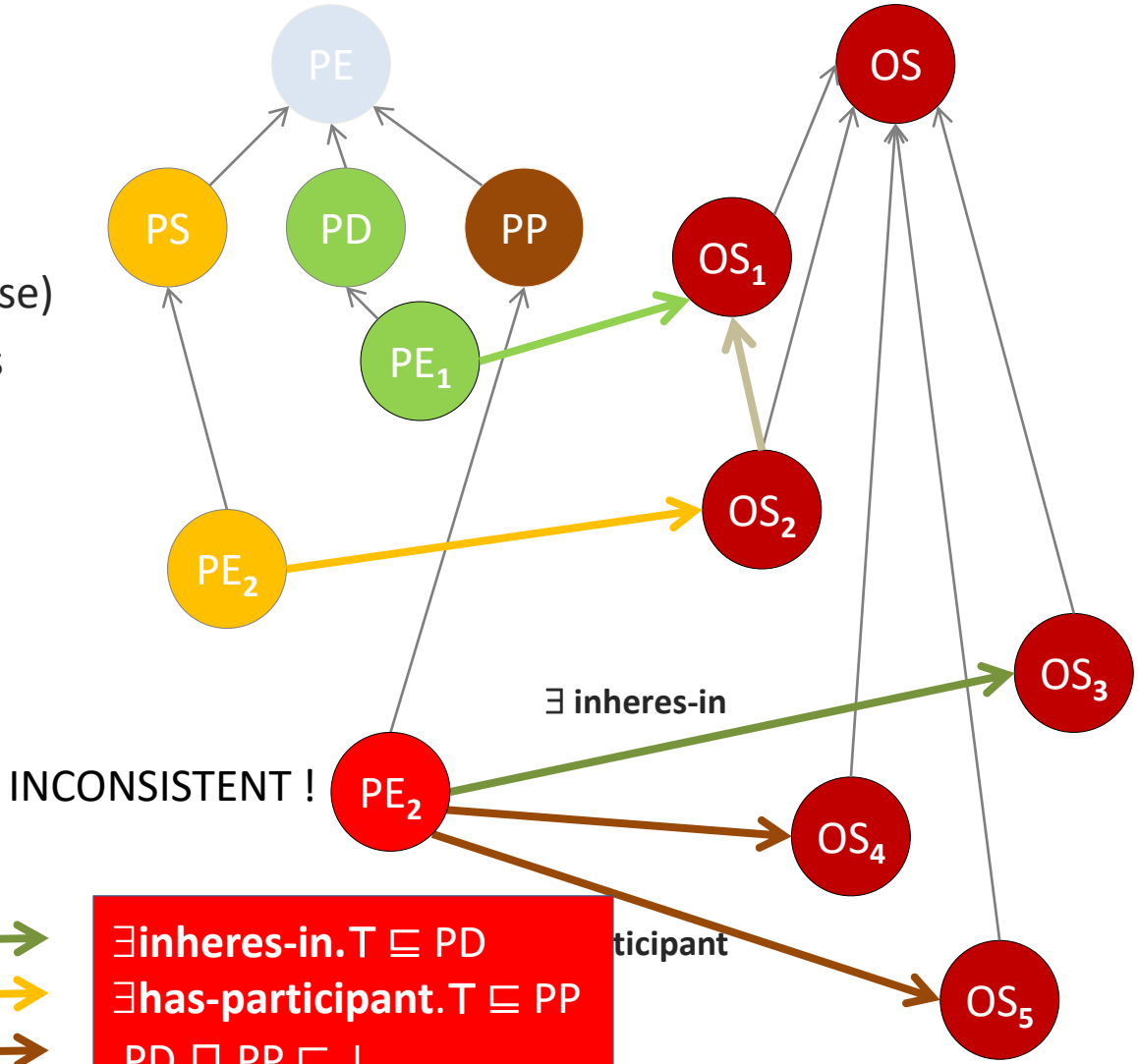

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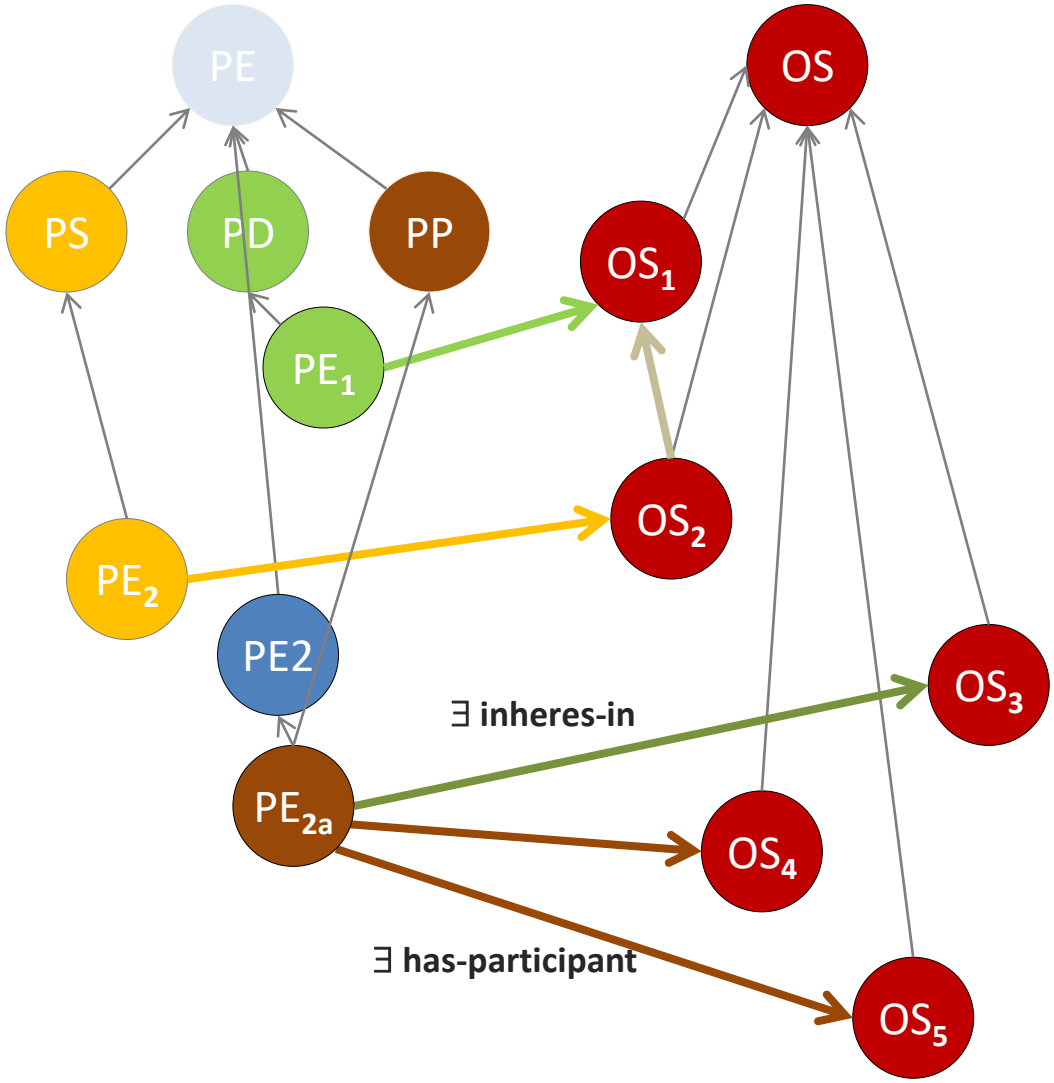

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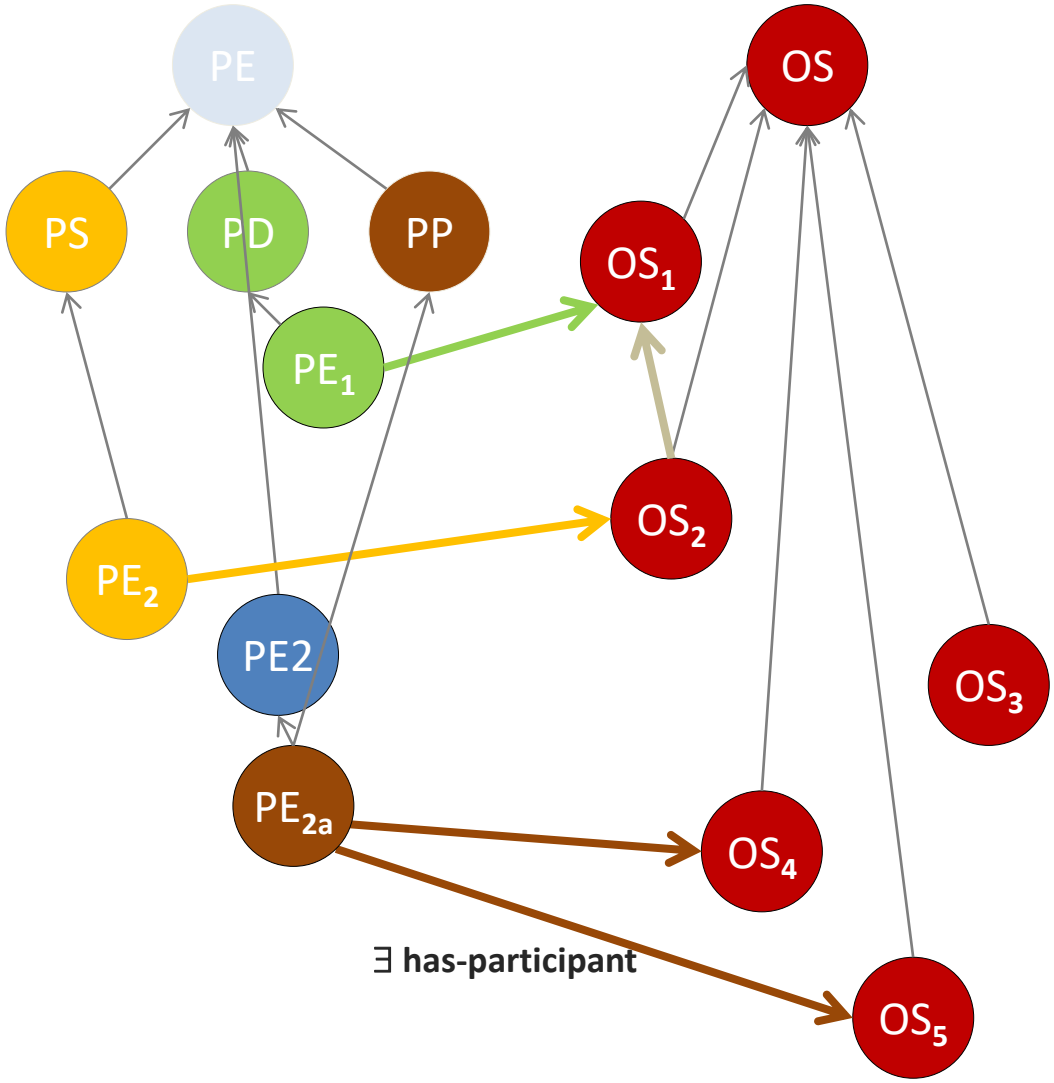

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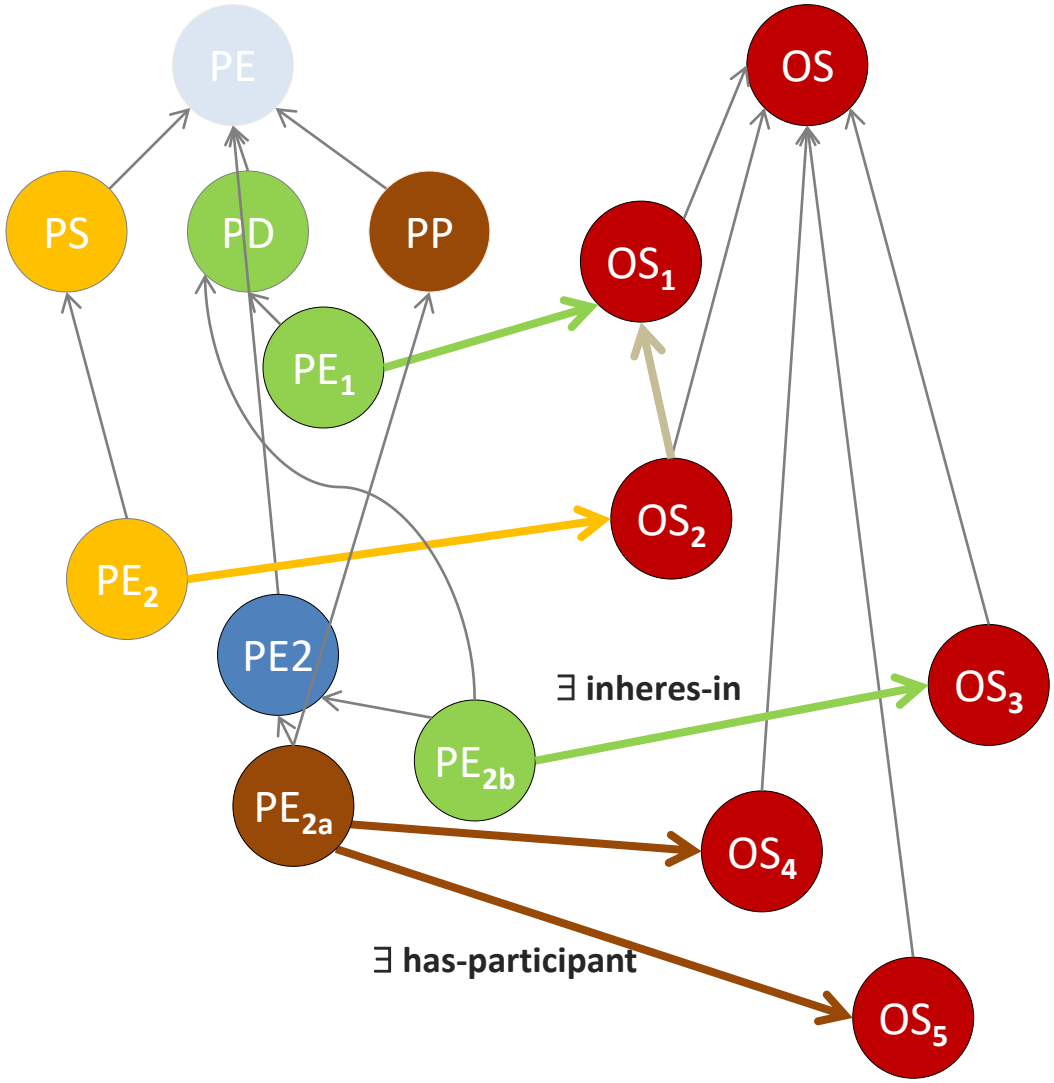

Conclusions

- "Disease": ontologically polymorphic category
- Refinement of disease classes into pathological structures, pathological dispositions, and pathological processes often not necessary
- Introduction of umbrella category *Pathological entity*, together with the high-level relation **has-locus**:
  - construction of simple model which already supports important inferences
  - permits graceful evolution towards more sophisticated models in which the above distinctions are introduced where necessary
- Implemented in BioTop (http://purl.org/biotop) and under discussion at IHTSDO for SNOMED CT

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DFG, grant agreement JA 1904/2-1, SCHU 2515/1-1 GoodOD (Good Ontology Design).

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