ONTOLOGICAL MODELLING AND REASONING OF PHENOTYPES

JOWO/ODLS, September 2019, Graz
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Agenda

1. Motivation
2. Smart Medical Information Technology for Healthcare (SMITH)
3. PhenoMan Integration in SMITH
4. Core Ontology of Phenotypes (COP)
5. Phenotype Algorithm Specification Ontologies (PASO)
6. Phenotype Manager (PhenoMan)
7. Conclusion
Motivation

successful determination and analysis of phenotypes plays a key role in:

- diagnostic process
- evaluation of risk factors
- recruitment of participants for clinical and epidemiological studies
- computable phenotype algorithms to solve these tasks are required

Goals

- machine-interpretable definition of the phenotype notion
- novel ontology-based method and tool to model and calculate phenotypes

standardized phenotype specification | phenotype reasoning based on instance data
Smart Medical Information Technology for Healthcare (SMITH)

- The main goal of the German Medical Informatics Initiative (MII) is making clinical data available for research
- SMITH is one of four funded consortia
Smart Medical Information Technology for Healthcare (SMITH)

- The main goal of the German Medical Informatics Initiative (MII) is making clinical data available for research
- SMITH is one of four funded consortia
- A phenotyping pipeline (PheP) will be established to systematically develop, evaluate and execute validated algorithms and models for classifying and annotating patient data based on routine electronic health records (EHR)
  - triggering alerts and actions
  - data sharing and deep analyses of patient care and outcomes
  - phenotype engines and factories required to specify, set up and execute phenotype algorithms
PhenoMan Integration in SMITH

PhenoMan API

- COP
  - PASO1
  - PASO2
  - PASO3

PhenoMan Service

Phenotype Designer
- create phenotypes

Phenotype Editor

Metadata Manager
- create metadata

ART-DECOR®

HDS schema

FHIR subscriptions / FHIR search

FHIR resources

calculated phenotypes (observation resources)

FHIR Server

HDS

Sources (last access: 2019-09-16):
https://www.hl7.org/fhir/
https://art-decor.org
ONTOLOGICAL MODELLING OF PHENOTYPES
Core Ontology of Phenotypes (COP)

- Phenotype vs. Phenotype Class
- Single vs. Composite Phenotypes
- Restricted vs. non-Restricted Phenotype Classes
Phenotype Algorithm Specification Ontologies (PASO)

- Model specific phenotypes (algorithms) using the COP
- Are embedded in the COP
  - the classes of the PASO are subclasses of the COP classes
  - every PASO subclass of the COP classes cop:Single_Phenotype, cop:Combined_Phenotype or cop:Derived_Phenotype is a phenotype class and is instantiated by phenotypes
  - direct subclasses are non-restricted, while the subclasses of the non-restricted phenotype classes are restricted
Example: BMI-PASO

<table>
<thead>
<tr>
<th>Age: &gt;=18; &lt;34</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI: &lt;19</td>
<td>BMI: &gt;=19; &lt;25</td>
<td>BMI: &gt;=25; &lt;30</td>
<td>BMI: &gt;=30</td>
<td></td>
</tr>
<tr>
<td>Age: &gt;=34</td>
<td>BMI: &lt;19</td>
<td>BMI: &gt;=19; &lt;27</td>
<td>BMI: &gt;=27; &lt;30</td>
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</table>
Example: BMI-PASO

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Example: BMI-PASO

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Underweight</th>
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<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: &gt;=18; &lt;34</td>
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<td>BMI: &gt;=30</td>
</tr>
</tbody>
</table>

Example: BMI - PASO

Phenotype
- Composite_Phenotype
  - Combined_Phenotype
    - Weight_status
      - Normal_weight
      - Obese
      - Overweight
      - Underweight
  - Derived_Phenotype
    - BMI
      - BMI_s_ge_19_0_l_25_0
      - BMI_s_ge_19_0_l_27_0
      - BMI_s_ge_25_0_l_30_0
      - BMI_s_ge_27_0_l_30_0
      - BMI_s_ge_30_0
      - BMI_s_l_19_0
  - Single_Phenotype
    - Age
      - Age_s_ge_18_l_34
    - Height
    - Weight

Equivalent To

```
Age
and (has_value some xsd:decimal[>= 34])
```
Example: BMI-PASO

<table>
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<tr>
<th>Age: &gt;=18; &lt;34</th>
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Example:
BMI - PASO

Phenotype
- Composite_Phenotype
- Combined_Phenotype
  - Weight_status
    - Normal_weight
    - Obese
    - Overweight
    - Underweight
- Derived_Phenotype
  - BMI
    - BMI_s_ge_19_0_l_25_0
    - BMI_s_ge_19_0_l_27_0
    - BMI_s_ge_19_0_l_27_0
    - BMI_s_ge_25_0_l_30_0
    - BMI_s_ge_27_0_l_30_0
    - BMI_s_ge_30_0
    - BMI_s_l_19_0
- Single_Phenotype
  - Age
    - Age_s_ge_18_l_34
    - Age_s_ge_34

General class axioms:
(has_part some Height) and (has_part some Weight) SubClassOf BMI

Equivalent To:
Age and (has_value some xsd:decimal[>= 34])

Formula:
Weight/Height^2

Main_title:
BMI

Variable:
- Height
- Weight

Universitat Leipzig
Example: BMI-PASO

<table>
<thead>
<tr>
<th></th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
</thead>
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<tr>
<td><strong>Age: &gt;=18; &lt;34</strong></td>
<td>BMI: &lt;19</td>
<td>BMI: &gt;=19; &lt;25</td>
<td>BMI: &gt;=25; &lt;30</td>
<td>BMI: &gt;=30</td>
</tr>
<tr>
<td><strong>Age: &gt;=34</strong></td>
<td>BMI: &lt;19</td>
<td>BMI: &gt;=19; &lt;27</td>
<td>BMI: &gt;=27; &lt;30</td>
<td>BMI: &gt;=30</td>
</tr>
</tbody>
</table>

Example:
BMI - PASO

Phenotype
  - Composite_Phenotype
    - Normal_weight
    - Obese
    - Overweight
    - Underweight
  - Derived_Phenotype
    - BMI
      - BMI_s_ge_19_0_l_25_0
      - BMI_s_ge_19_0_l_27_0
      - BMI_s_ge_25_0_l_30_0
      - BMI_s_ge_27_0_l_30_0
      - BMI_s_ge_30_0
      - BMI_s_ge_31_0

General class axioms
(has_part some Height) and (has_part some Weight) SubClassOf BMI

Equivalent To
BMI
and (has_value some xsd:decimal[>= 25.0, < 30.0])

Equivalent To
Age
and (has_value some xsd:decimal[>= 34])
Example: BMI-PASO

<table>
<thead>
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<td>BMI: &gt;=19; &lt;27</td>
<td>BMI: &gt;=27; &lt;30</td>
<td>BMI: &gt;=30</td>
</tr>
</tbody>
</table>

**General class axioms**

\[
((\text{has part some Age}_s \text{ ge 18 l 34}) \text{ and } (\text{has part some BMI}_s \text{ ge 19 0 l 25 0})) \text{ or } ((\text{has part some Age}_s \text{ ge 34}) \text{ and } (\text{has part some BMI}_s \text{ ge 19 0 l 27 0})) \text{ SubClassOf Normal weight}
\]

**General class axioms**

\[
(\text{has part some Height}) \text{ and } (\text{has part some Weight}) \text{ SubClassOf BMI}
\]

**Equivalent To**

\[
\text{BMI} \text{ and } (\text{has value some xsd:decimal[}>= 25.0, < 30.0])
\]

**Equivalent To**

\[
\text{Age} \text{ and } (\text{has value some xsd:decimal[}>= 34))
\]
TECHNICAL ASPECTS OF THE PHENOTYPE MANAGER (PHENOMAN)
Phenotype Manager (PhenoMan)
Phenotype Manager (PhenoMan)

```
"resourceType": "Observation",
"id": "162209",
"meta": {
  "versionId": "1",
  "lastUpdated": "2019-08-26T11:10:19.353+00:00"
},
"code": {
  "coding": [
    {
      "system": "http://loinc.org",
      "code": "3141-9",
      "display": "Body weight"
    },
    {
      "system": "http://snomed.info/sct",
      "code": "27113001",
      "display": "Body weight (observable entity)"
    }
  ]
},
"subject": {
  "reference": "Patient/157411"
},
"effectiveDateTime": "2019-08-26T13:09:58+02:00",
"valueQuantity": {
  "value": 75.0,
  "unit": "kg",
  "system": "http://unitsofmeasure.org",
  "code": "kg"
}
```

HL7 FHIR Resource of weight observation as JSON
Phenotype Manager (PhenoMan)

- Implements a multistage reasoning approach combining standard reasoners (e.g., Pellet or HermiT) and mathematical calculations
- Receives instance data set from a FHIR Server as FHIR resources, interprets and inserts it into the ontology

```
"resourceType": "Observation",
"id": "162209",
"meta": {
  "versionId": "1",
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},
"code": {
  "coding": [
  {
    "system": "http://loinc.org",
    "code": "3141-9",
    "display": "Body weight"
  },
  {
    "system": "http://snomed.info/sct",
    "code": "27113001",
    "display": "Body weight (observable entity)"
  }
  ],
  "system": "http://loinc.org",
  "code": "29463-7",
  "display": "Body weight"
},
"subject": {
  "reference": "Patient/157411"
},
"effectiveDateTime": "2019-08-26T13:09:58+02:00",
"valueQuantity": {
  "value": 75.0,
  "unit": "kg",
  "system": "http://unitsofmeasure.org",
  "code": "kg"
}
```

HL7 FHIR Resource of weight observation as JSON
Phenotype Manager (PhenoMan)

- Implements a multistage reasoning approach combining standard reasoners (e.g., Pellet or HermiT) and mathematical calculations
- Receives instance data set from a FHIR Server as FHIR resources, interprets and inserts it into the ontology
  - individual properties (single phenotypes) as instances of the direct subclasses of cop:Single_Phenotype (e.g., Weight, Height) with property assertions (e.g., “has_value 75” for Weight)
  - a composite phenotype as instance of the class cop:Composite_Phenotype, which combines all the single phenotype instances using has_part property assertions

```json
"resourceType": "Observation",
"id": "162209",
"meta": {
  "versionId": "1",
  "lastUpdated": "2019-08-26T11:10:19.353+00:00"
},
"code": {
  "coding": [
    {
      "system": "http://loinc.org",
      "code": "3141-9",
      "display": "Body weight"
    },
    {
      "system": "http://snomed.info/sct",
      "code": "27113001",
      "display": "Body weight (observable entity)"
    }
  ]
},
"subject": {
  "reference": "Patient/157411"
},
"effectiveDateTime": "2019-08-26T13:09:58+02:00",
"valueQuantity": {
  "value": 75.0,
  "unit": "kg",
  "system": "http://unitsofmeasure.org",
  "code": "kg"
},

HL7 FHIR Resource of weight observation as JSON
PhenoMan Execution Example (BMI) - I

1. Classification step
   - the single phenotype instances are classified in restricted classes (age ranges)

   ![Equivalent To](Age
   and (has_value some xsd:decimal[>= 34]))

   - the composite phenotype instance is classified in composite phenotype classes (BMI)

   ![General class axioms](has_part some Height) and (has_part some Weight) SubClassOf BMI
PhenoMan Execution Example (BMI) - I

1. Classification step
   - The single phenotype instances are classified in restricted classes (age ranges)
   - The composite phenotype instance is classified in composite phenotype classes (BMI)

Age = 40 years
Height = 1.7 m
Weight = 75 kg
PhenoMan Execution Example (BMI) - I

1. Classification step
   - the single phenotype instances are classified in restricted classes (age ranges)
   - the composite phenotype instance is classified in composite phenotype classes (BMI)
PhenoMan Execution Example (BMI) - II

2. Calculation step

- the formula of the derived phenotypes is calculated (BMI)
- a BMI instance with the calculated value (≈ 26) is added to the composite phenotype instance


### PhenoMan Execution Example (BMI) - II

**Calculation step**
- the formula of the derived phenotypes is calculated (BMI)
- a BMI instance with the calculated value ($\approx 26$) is added to the composite phenotype instance

**Composite Phenotype**

- Age = 40 years
- Height = 1.7 m
- Weight = 75 kg
2. Calculation step
   - the formula of the derived phenotypes is calculated (BMI)
   - a BMI instance with the calculated value (≈ 26) is added to the composite phenotype instance

**PhenoMan Execution Example (BMI) - II**

**Composite Phenotype**

- Age = 40 years
- Height = 1.7 m
- Weight = 75 kg
- BMI ≈ 26 kg/m²
PhenoMan Execution Example (BMI) - III

3. Classification step
   - the BMI instance is classified in restricted classes (BMI ranges)
     - Equivalent To
       - BMI
         and (has_value some xsd:decimal[>= 19.0, < 27.0])
     - BMI
       and (has_value some xsd:decimal[>= 25.0, < 30.0])
   - the weight status is derived based on age und BMI range
     - General class axioms
       - ((has_part some Age_s_ge_18_l_34) and (has_part some BMI_s_ge_19_0_l_25_0)) or
         ((has_part some Age_s_ge_34) and (has_part some BMI_s_ge_19_0_l_27_0))
       SubClassOf Normal_weight
PhenoMan Execution Example (BMI) - III

3. Classification step
   - the BMI instance is classified in restricted classes (BMI ranges)
     Equivalent To
     \[
     \text{BMI} \quad \text{has_value some xsd:decimal[} \geq 19.0, < 27.0]\]
     
     Equivalent To
     \[
     \text{BMI} \quad \text{has_value some xsd:decimal[} \geq 25.0, < 30.0]\]
     
     - the weight status is derived based on age and BMI range

General class axioms
\[
((\text{has_part some Age_s_ge_18_1_34}) \text{ and } (\text{has_part some BMI_s_ge_19_0_1_25_0})) \text{ or } ((\text{has_part some Age_s_ge_34}) \text{ and } (\text{has_part some BMI_s_ge_19_0_1_27_0}))
\]
SubClassOf Normal_weight
PhenoMan Execution Example (BMI) - III

3. Classification step
   - the BMI instance is classified in restricted classes (BMI ranges)
     - Equivalent To
       ```
       BMI
       and (has_value some xsd:decimal[>= 19.0, < 27.0])
       ```
   - the weight status is derived based on age und BMI range
     - Equivalent To
       ```
       BMI
       and (has_value some xsd:decimal[>= 25.0, < 30.0])
       ```
   - General class axioms
     ```
     (((has_part some Age_s_ge_18_l_34) and (has_part some BMI_s_ge_19_0_l_25_0)) or
     (((has_part some Age_s_ge_34) and (has_part some BMI_s_ge_19_0_l_27_0)))
     SubClassOf Normal_weight
     ```
PhenoMan Execution Example (BMI) - IV

- Classification and calculation steps can be repeated several times until all formulas are calculated and all phenotypes are classified
  - if a non-restricted phenotype class has subclasses, which are in turn used in combined phenotypes
PhenoMan Execution Example (BMI) - IV

- Classification and calculation steps can be repeated several times until all formulas are calculated and all phenotypes are classified
  - if a non-restricted phenotype class has subclasses, which are in turn used in combined phenotypes
- PhenoMan writes the results (calculated or derived phenotypes) as observations back to the FHIR server

```
"resourceType": "Observation",
"id": "162211",
"meta": {
  "versionId": "1",
  "lastUpdated": "2019-08-26T11:13:46.102+00:00"
},
"code": {
  "coding": [
    {
      "system": "http://snomed.info/sct",
      "code": "60621009",
      "display": "Body mass index (observable on"
    }
  ]
},
"subject": {
  "reference": "Patient/157411"
},
"effectiveDateTime": "2019-08-26T11:13:27+02:00",
"valueQuantity": {
  "value": 25.95155709342561,
  "system": "http://unitsofmeasurement.org"
},
"method": {
  "coding": [
    {
      "system": "http://www.smith.org/phenoman",
      "code": "phenoman_0.2.7",
      "display": "generated by Phenotype Manager"
    }
  ]
}
```

HL7 FHIR Resource of BMI observation as JSON
Creating PASOs with the Phenotype Editor

![Phenotype Editor interface](image)

Ontology: SOFA

- Search for phenotype...
  - Phenotype Category
  - Laboratory
  - Medication
  - Nervous System
  - Respiratory System
  - Score System
    - GCS
    - SOFA
      - SOFA Cardiovascular System Score
      - SOFA Cardiovascular System Score 1
      - SOFA Cardiovascular System Score 2
      - SOFA Cardiovascular System Score 3
      - SOFA Cardiovascular System Score 4
      - SOFA Coagulation Score
      - SOFA Kidneys Score
      - SOFA Liver Score
      - SOFA Nervous System Score
      - SOFA Respiratory System Score
      - SOFA Score

Identifier: SOFA_Cardiovascular_System_Score_3

Primary Title: SOFA Cardiovascular System Score 3

Restriction:

**Boolean Expression**

- Dopamine In \(> 5.0, \leq 15.0\) \(\mu\)g/kg/min
- Epinephrine \(\leq 0.1\) \(\mu\)g/kg/min
- Norepinephrine \(\leq 0.1\) \(\mu\)g/kg/min

Drag-and-drop phenotypes from the right side into your expression.

By Score:

3

Description about scores:

SAVE RESTRICTED COMPOSITE BOOLEAN PHENOTYPE
Conclusion

- Novel ontology-based method to model phenotypes for **automated phenotype reasoning based on instance data** (e.g., patient data)
- Iterative reasoning approach, which **combines classification tasks with mathematical calculations** at runtime
- Can be used in **clinical context**, e.g., for supporting the diagnostic process or recruiting appropriate participants for studies
- Successfully evaluated
  - some algorithms (such as socio-economic status) were evaluated in comparison with the corresponding SPSS derivatives based on the research database of the LIFE study
THANK YOU FOR YOUR ATTENTION!

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Christoph.Beger@imise.uni-Leipzig.de
Implementation

PhenoMan:
- OWL API, HermiT, Openllet
- For calculations: Java Expression Evaluator (EvalEx)
  - enables evaluating mathematical and Boolean (e.g., Boolean operators and IF-THEN-ELSE structures) expressions
  - supports defining custom functions and operators.

Phenotype Editor:
- Desktop app designed with JavaScript and shipped as cross platform Electron app with an integrated lightweight web browser (Chromium)
- Backend service provides information and management functionalities of a PASO via REST interface (DropWizard), serves as a mediator to the PhenoMan API

Prototype available on GitHub (GPL-3.0):
https://github.com/ChristophB/ontology_service
https://github.com/ChristophB/phenotype_editor