Development of Description Framework of Pharmacodynamics Ontology and its Application to Possible Drug-drug Interaction Reasoning

Takeshi IMAI, Ph.D
Masayo Hayakawa
Kazuhiko OHE, MD, Ph.D

The University of Tokyo Hospital, JAPAN
Outline

1. Background & Objectives
2. Description framework of pharmacodynamics ontology
3. Application to possible DDI reasoning
4. Experimental results
5. Discussion, limitations and future directions
Background

• Combination of drugs sometimes induces synergistic or antagonistic effects. Some of such drug-drug interactions (DDIs) may cause serious adverse events.

• DDI information is currently not been well utilized in daily clinical practice.
  – Could have been caused by the lack of consistency in DDI information in the Summaries of Product Characteristics (SPCs) of drugs. (Virty ’97)

• It’s necessary to develop a new methodology...
  – which leverages machine reasoning and knowledge base to provide DDI information with reasons and certainty
  – regardless of the descriptions in SPCs
  – Ontology is considered to be one effective solutions to describe knowledge formally
Objectives

1) To develop a description framework of pharmacodynamics ontology that is necessary for machine reasoning to identify possible DDI pairs based on pharmacodynamic mechanisms. **[Out of Scope]:**
   - Pharmacokinetic interactions
   - Drugs like antiseptics that directly act against the target.
     - Focusing on signal transduction mechanisms and resultant physiological systems.

2) To develop a methodology to identify different types of possible DDI pairs based on the ontology and to investigate the effectiveness in an example domain.
Description framework of pharmacodynamics ontology
Fundamental model of Pharmacodynamics DDIs
- three-layered model -

**Medicine**

- Single drug molecules
- "target sub-process"

**Signal Transduction Process (STP)**

- Promoting
- or
- Inhibiting
- "target process"

**Physiological Chain (PC)**

- "physiological Response"
- Physiological state
- Physiological chain

Pharmacological effect
Fundamental model of Pharmacodynamics DDIs - the three-layered model -

**Medicine**

- "Propranolol Hydrochloride"

**Signal Transduction Process (STP)**

- "Propranolol"
- "Bind on the cell membrane"

**Physiological Chain (PC)**

- "Noradrenaline STP"
- "Blood Pressure Decrease"

*Signal Transduction Process (STP)*

- "target sub-process"

*Physiological Chain (PC)*

- "Physiological state"
- "Physiological Response"
Pharmacodynamic DDIs will then occur on several points!
Fundamental model of Pharmacodynamics DDIs - three-layered model -

Two different “Single drug molecules” (A, B) act on the same “STP” (C) or the same sub-process (D)

→ The resultant effect of DDI will be synergistic or antagonistic
Even when the targeting STPs are different (C, D), the pair (A & B) could be a possible DDI,

(1) if the physiological responses are the same (E)
(2) or included in the same physiological chain (E, F)
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(1) if the physiological responses are the same (E)
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Ontological representation (using ‘HOZO’ editor)
Application to possible DDI reasoning
Framework to identify possible DDIs

[Rule]: A pair of two drugs will be identified as a possible DDI, if any combination of “single drug molecules” of those drugs has the interaction that matches one of the 14 DDI types.

Five basic types of DDI

<table>
<thead>
<tr>
<th>DDI type</th>
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<th>Sub-process</th>
<th>Physiological response</th>
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<tbody>
<tr>
<td>Type1</td>
<td>Same</td>
<td>Different</td>
<td>In the same PC</td>
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</tr>
<tr>
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</tr>
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Example domain & Experimental settings

- Drugs related to **noradrenaline STP**
  - Noradrenaline is a representative among various chemical mediators

- Extracted **89 single drug molecules (SDM)** related to **noradrenaline STP** from Japanese Drug Database (JAMES)

- Pharmacodynamics information for each SDM was manually analyzed and added into the ontology as subordinate classes.

- A pharmacology expert reviewed all the combinations of those SDMs, and extracted possible DDI pairs according to the extraction rule.
Experimental Result
Each pair has at least one interaction point (‘light gray cell’) that provides information about the reason why the pair was considered as a possible DDI in terms of pharmacodynamics mechanisms.
Possible DDIs were not found for three sub-types (2i, 4p, 4i)

- For [Type 2i]:
  - all SDMs acting on noradrenaline STP with “inhibition” effect have the same physiological response (“blood pressure decrease”)

- For [Type 4i]:
  - Very few cases... BUT..

### [Type4A]

**Same STP, same Sub-Process, but different Physiological responses**

- **Clonidine hydrochloride**
- **Mianserin hydrochloride**

**Antagonistic**

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**For [Type 2i]:**
- all SDMs acting on noradrenaline STP with "inhibition" effect have the same physiological response ("blood pressure decrease")

**For [Type 4i]:**
- Very few cases... BUT..
Another interesting example: Type 5S

- These two SDMs don’t share the same target STP and sub-process of STP.
- Physiological responses are not the same.
- But extracted as possible DDI (synergistic).

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- **Spironolactone**: Aldosterone STP, Aldosterone receptor
- **Propranolol hydrochloride**: Noradrenaline STP, Beta1 adrenergic receptor

Process:
- Excretion of sodium
- Decrease in blood volume
- Decrease in cardiac output
- Blood pressure decrease
Discussion (1)

• **11 different types** of possible DDIs were identified with supporting information of DDI mechanisms.
  – Useful to understand contraindications

  **Comparison with SPCs in Japan**
  – 31% of all combinations were described
  – There is no gold standard of ‘true DDI pairs’ ...
  – At least SPCs in Japan also have inconsistency (60%)

• For large-scale monitoring of drug safety (EU-ADR, etc.)
  – ‘Distinguishability’ and ‘Explanation capability’ would be useful

- **Distinguishability**
- **Explanation capability**
Discussion (2)

- Comparison with preceding researches
  - DrugBANK, PharmGKB, KEGG
    - Contains a lot of information about pharmacodynamics pathways
    - DDI information is not formally described (Natural language)
  - Drug Interaction Ontology (DIO)
    - Fundamental framework for inferences of drug-biomolecule interactions like our approach

Corresponding to the information of “STP layer”

Do not contain or formally describe “the causal chains of physiological states”

Necessary for the detection of possible DDI pairs of Type 1, 3 and 5!

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Limitations & future tasks

• Limitations:
  – Pharmacokinetics is out of the scope
  – Tested on a limited domain

• Future tasks:
  – To expand our ontology and to cover other types of DDIs.
  – A new methodology to accumulate a lot of knowledge efficiently.
Acknowledgement

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Thank you for attention!

• Questions & Discussion

• Contact

Takeshi IMAI, Ph.D
The University of Tokyo Hospital, JAPAN
ken@hcc.h.u-tokyo.ac.jp