uc_FIDO: unambiguous characterization of food interactions with drugs ontology

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***Abstract*— uc_FIDO is an ontology that unambiguously characterizes food interactions with drugs in the human body. This ontology is part of a group of food ontologies describing food and the human experience at the International Center for Food Ontology Operability, Data and Semantics (IC-FOODS) at UC Davis. The first of its kind, uc_FIDO characterizes relations between food, medicine, and human health. uc_FIDO brings together several existing ontologies related to anatomy, metabolic pathways, biological processes, drug ingredients and food structures. Through these ontologies, uc_FIDO annotates relationships between food and drug bioactives, human physiological conditions, and biological reaction pathways. Relationships that link together fully characterize various food interactions with drugs and their effects.**

The current dearth of ontologies for characterizing foods limits advancement of informatics solutions for improving health. As ontologies of foods are developed, it becomes necessary to describe ingredients, bioactive molecules, potential toxins, and other molecules in food interacting with drugs and the human body.

Keywords—bioactive; interaction; metabolic process; active drug ingredient; food component; food matrix

I. Introduction (*Motivation and intended usage*)

Approximately seven percent of hospitalizations are the result of adverse drug reactions [1], many of which occur between drugs and food. Past research clarifies these potentially deadly reactions between our food and medicine. Examples include interactions between grapefruit and drugs which alter pathways involving cytochrome P450 (CytP450). Drugs such as Lipitor (atorvastatin, a cholesterol-lowering drug) were found in dangerously high concentrations in the bloodstream when consumed with grapefruit juice [2]. Drugs also limit nutrient absorption from many foods. Corticosteroids, for example, are linked to increased calcium excretion from the body [3]. These examples merely highlight the broad array of effects and sources involved in food-drug interactions. Much research has been undertaken, yet no knowledge repository captures the scope of food-drug related interactions, adverse, favorable, or otherwise. uc_FIDO provides a platform upon which development of ecosystems of consumer tools surrounding foods, drugs, and education can be built to unify information resources. This will be crucial in discovering and understanding all pharmacological, nutritional, and drug efficacy effects of these interactions.

uc_FIDO is designed as part of IC-FOODS, a larger network of unambiguously characterized food ontologies meant to connect bridges between food systems, food and health [4].

II. Design and Methods

A. Scope and Knowledge Elicitation

uc_FIDO encompasses multiple ontologies and exclusively contains nearly forty thousand axioms and over two thousand classes. Ontologies are integrated via Protégé 5.0.0.24 and updated versions of uc_FIDO are uploaded to GitHub. Within uc_FIDO, food and drug interaction modelers can utilize various base ontologies. For drug active ingredients and chemical interactions, the Drug Ontology [5], [6] CheBI and ingredient sub-ontologies provide a foundation to describe drugs' effects and active ingredients. uc_Eating [7] defines eating behaviors for various situations, which is crucial to establishing a basis of foods in the human body because psychological behavior affects food selection [8].

Multiple linkages formed within base ontologies create different food-drug interactions. Each food-drug interaction in the ontology maps sub-classes relating to food bioactive ingredients, drug bioactives, and human body pathways that make up food-drug interactions. Interactions, bioactives, and pathways are the primary classes that link together to build and characterize interactions. Subclasses that have properties linking to each other create defined interactions and serve as primary classes within uc_FIDO.

Active ingredients primarily compose the class hierarchy drawn from drug and food ontologies. However, because uc_FIDO is intended as a knowledge source for consumer-friendly tools, features like brands become necessary to define as sub-classes. Because of the multiple properties of different foods based on food matrices, concentrations of nutrients in different ingredients (ie. Skim milk vs. whole milk), each food becomes a specific class with multiple subclasses relating to that food. For example, the class "sourdough" would have subclasses relating to ingredients ("all-purpose_flour"), recipes, bioactive molecules, and nutrition content. Bioactive molecules and nutrients react with drug bioactives in the human body, and thus are crucial to mapping out defined interactions.

The location and stimuli of human body reactions require full comprehension. Understanding these is crucial to building uc_FIDO. Specifically, most reactions occur in the blood stream, the blood-brain barrier, and in organs. Defining these reactions, nutrient cycles, and biological pathways that are affected by these potential interactions is crucial. Biological pathways are much more complex based on anatomy and location. uc_FIDO draws from Uberon as a class resource for anatomical structures and locations, while Reactome integrates base ontologies of biological pathways [9]. From here, human body reaction pathways like "sensory_process" or "mechanical_food_breakdown" and anatomical locations including "lung", "alveoli", and others, become key classes that link to where drug and food bioactive compounds are metabolized by physiological location and anatomical structures where reactions occur. Through properties like physiological location and common reactants or products, interactions are defined by linking together different bioactives and conditions. For example, the class "bloodstream_interaction" links to the classes "Lipitor" and "Grapefruit" through sharing the property "has_location bloodstream".

B. *Ontology Mapping*

Mapping of uc_FIDO was undertaken similarly to Joslin's One-Carbon Metabolism map [10]. CMAPs initially mapped food drug interactions split into three components – food, drugs, and body reaction pathways.

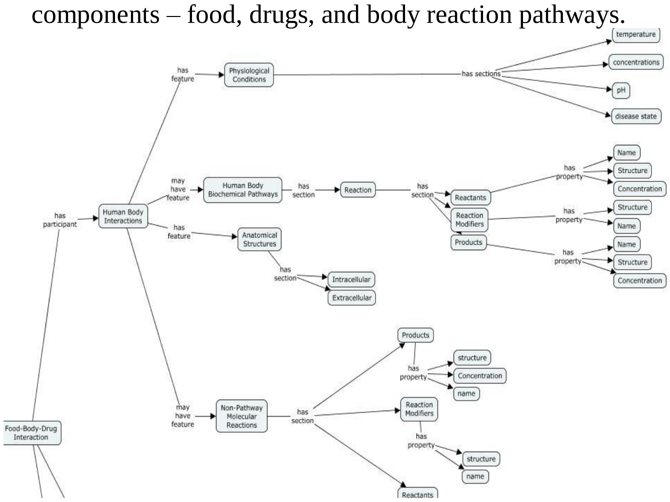

Figure 1. Concept Map generalizing but detailing components of human body reaction pathways in uc_FIDO.

Figure 1 above shows CMAPs effectively creating generalized previews of uc_FIDO. Each class of human body reactions above has subclasses like disease states, concentrations, and pH levels that all factor into whether reactions within food drug interactions will take place.

When translating the concept map into linkages and classes in Protégé, many extra subclasses are considered. Because of several potential sites of food-drug interactions [11], these must be taken into account when mapping out classes of interactions in base ontologies. Figure 2 below shows some subclasses considered because of the possible locations of food-drug interactions.

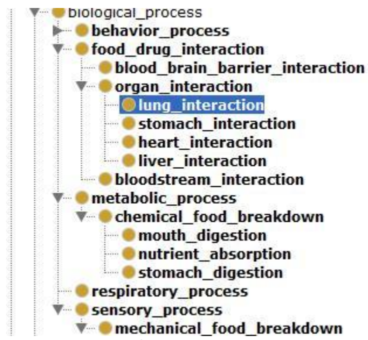

Figure 2. Examples of subclasses developed as part of the interaction class hierarchy for uc_FoodDrugInteractionOntology.

Linkages of these subclasses occur through sharing properties including anatomical location and reactant or product molecules. The sharing of properties between interactions, anatomical structures, and bioactive pathway sites allows for accurate mapping of where and how these interactions occur, along with their effects.

III. RESULTS AND ANALYSIS

The completion of uc_FIDO requires base ontologies currently under construction. Specifically, ontologies surrounding food need to be more developed. While several ontologies regarding food are progressing [11], no current food ontology takes into account all different types of bioactive compounds found in foods. Ingredients and food additives have been taken into account in some cases, but pesticides, natural food toxins, and other bioactives also need to be considered as they may have effects on drug efficacy or pharmacological effects. Additional factors (ie. other supplements or foods consumed) also factor into drug concentration bloodstreams, contributing to a network of multiple simultaneous interactions that requires further research. uc_FIDO is a great start for mapping relationships between drugs and other substances intravenous or extraneous to the human body, such as food. However, more ontologies need development to describe the relationship between nutrients and genes [10] or ontologies that understand how food and nutrients affect biological pathways and human reactions, along with other food related ontologies. When these ontologies are completed, actions of food and drugs within human bodies can be realized in a clean, easy-to-use ontology.

While uc_FIDO continues to be developed under IC-FOODS, ontologies described in the above paragraphs relating to all chemicals present in food and nutrient-gene interactions (among others) can be developed. When all IC-FOODS ontologies are completed, they can power multiple consumer and medical Internet applications that inform and promote quicker responses to food emergencies while increasing access to food education information.

References

[1] Jason Lazarou, Bruce H. Pomeranz, and Paul N. Corey, “Incidence of Adverse Drug Events in Hospitalized Patients: A Meta-Analysis of Prospective Studies,” *J. Am. Med. Assoc.*, vol. 279, no. 15, pp. 1200–1205, May 1998.

[2] Irina Piatkov, Trudi Jones, and Mark McLean, “Drug Interactions, Pharmacogenomics and Cardiovascular Complication,” *Intech*, 2013.

[3] RM Carney, KE Freedland, EH Rubin, MW Rich, BC Steinmeyer, and WS Harris, “Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial.,” *J. Am. Med. Assoc.*, vol. 302, no. 15, pp. 1651–1657, Oct. 2009.

[4] Matthew C Lange, Danielle G Lemay, and J Bruce German, “A Multi-ontology Framework to Guide Agriculture and Food towards Diet and Health,” *J. Sci. Food Agric.*, vol. 87, pp. 1427–1434, Apr. 2007.

[5] Unknown Author, “DrON Chebi.” Unpublished., 2015.

[6] Unknown Author, “DrON Ingredients Ontology.” Unpublished.

[7] Kimiya Taji and Matthew C. Lange, “uc_Eating: Ontology for unambigious characterization of eating and food habits.” Unpublished., 01-Jul-2016.

[8] F Bellisle, “Why should we study human food intake behaviour?,” *Nutr. Metab. Cardiovasc. Dis.*, vol. 13, no. 4, pp. 189–193, Aug. 2003.

[9] “Reactome BioPathway Software.” Unpublished.

[10] A. C. Joslin, R. Green, J. B. German, and M. C. Lange, “Concept mapping One-Carbon Metabolism to model future ontologies for nutrient–gene–phenotype interactions,” *Genes Nutr.*, vol. 9, no. 5, Sep. 2014.

[11] Maged N. Kamel Boulos, Abdulslam Yassine, Shervin Shirmohammadi, Chakkrit Snae Namahoot, and Michael Bruckner, “Towards an ‘Internet of Food’: Food Ontologies for the Internet of Things,” *Future Internet*, vol. 7, pp. 372–392, Oct. 2015.