BigChem ESR7 PhD Project

Mid-term Progress Report

Exploration of uncharted regions of chemical space by reaction-driven *de novo* design

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Overview

1. Introduction
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5. Conclusion and Outlook
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1. Introduction

张雪瑾 *Xuejin Zhang, or JJ,* **中国人**

25 years old, Bcs & Msc China Pharmaceutical University; worked at WuXi AppTec Co. 06.2015-07.2016.

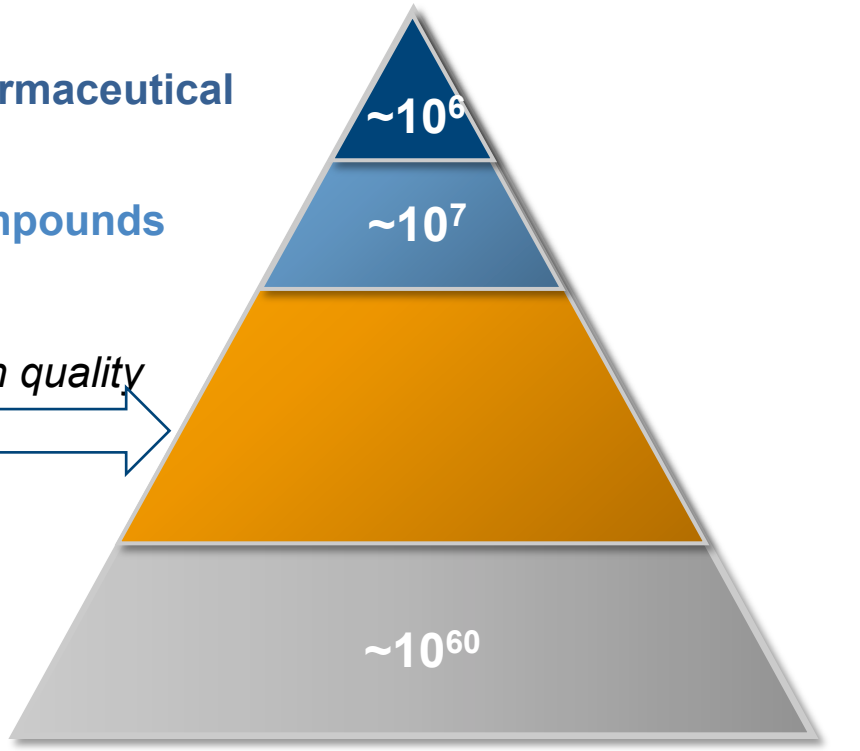
Currently is registered at ETHZ & working at BI (secondment).

Screening collection of pharmaceutical companies

Commercially available compounds

Synthetically accessible & high quality chemical space

Theoretical total chemical space



1. Introduction

Objectives of ESR7:

Bigger is not better:

- Implement an algorithm to translate multi-step organic synthesis protocols into a **high-quality & novel** chemical space of **synthetically accessible** molecules.

Clever Mining:

- Perform extensive data analysis to inspect the chemical space properties
- Quantitative comparison of this chemical space with available chemical libraries

Exploit future:

- Employ *de novo* design of compounds with a desired profile.

Proof-of-Concept:

- Synthesize & test.

2. Methodology

Open source software:

- RDKit: toolkit for cheminformatics
- Scikit learn: data mining, data analysis and machine learning in Python

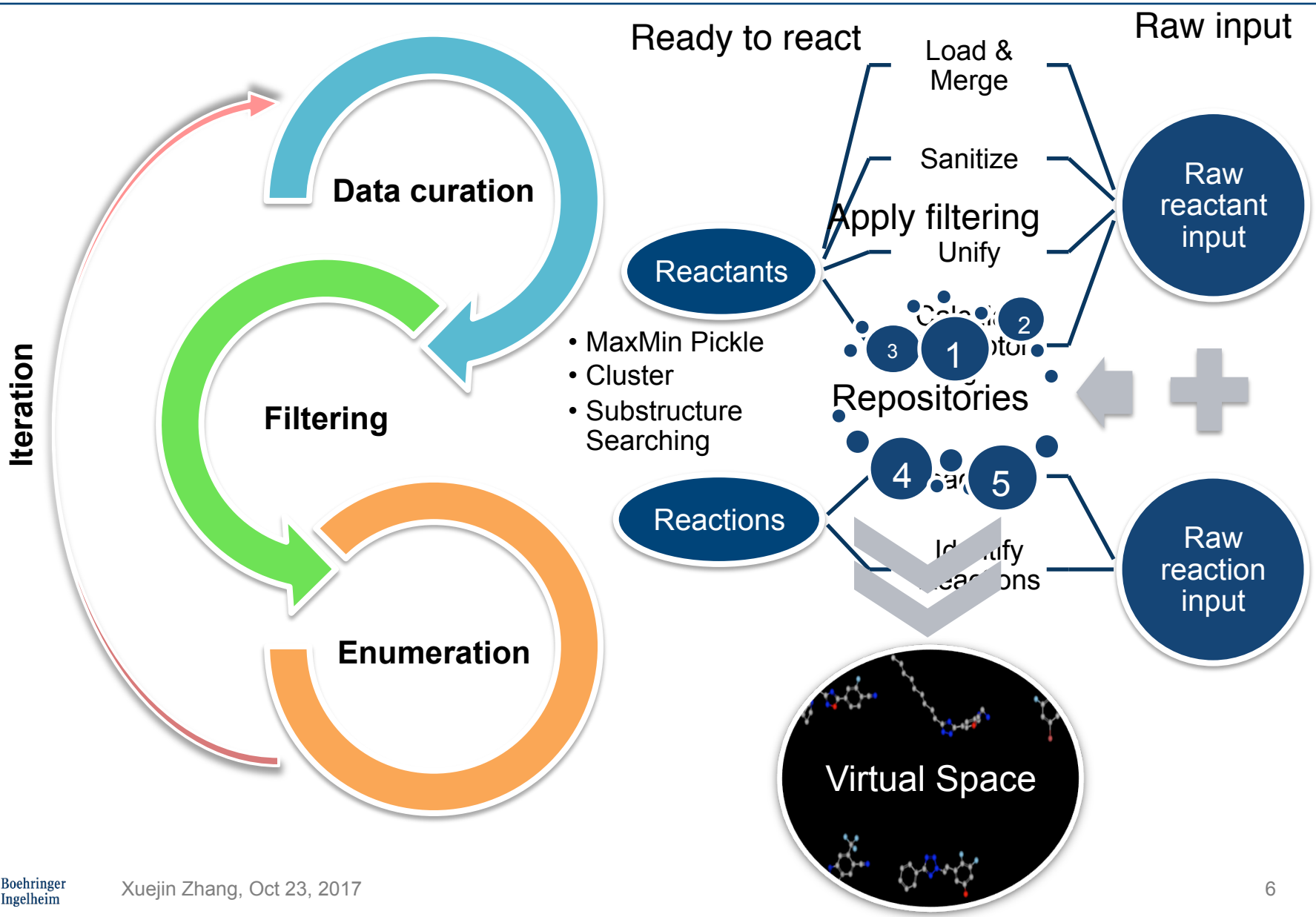
Chemical reactions:

- 209 reactions from ChemAxon reaction library
- *literature collection of most commonly used organic chemical reactions*

Reagents input source:

- *11045 reagents BIOVIA Available Chemicals Directory (ACD, MW <= 250 Da)*

3. Enumeration Software Cycle



3. Enumeration Software Features

- User friendly
  - Automatically enumeration after uploading input
  - Automatically calculation of molecular properties
  - Automatically generated graphic reports after enumeration

- Full flexibility
  - Predefined quality control rules & customized constraints on space generation

- Diverse methodologies
  - MaxMin diversity, clustering, random, MW, number heavy atoms etc.

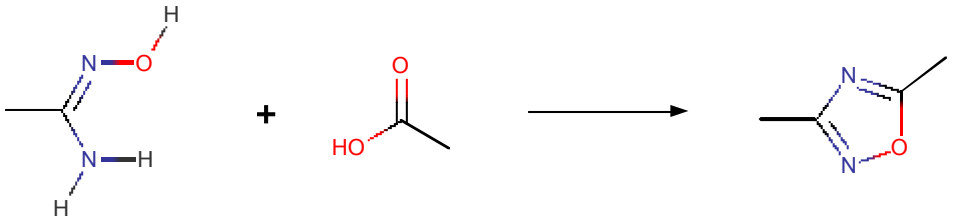
- Multiprocessing jobs

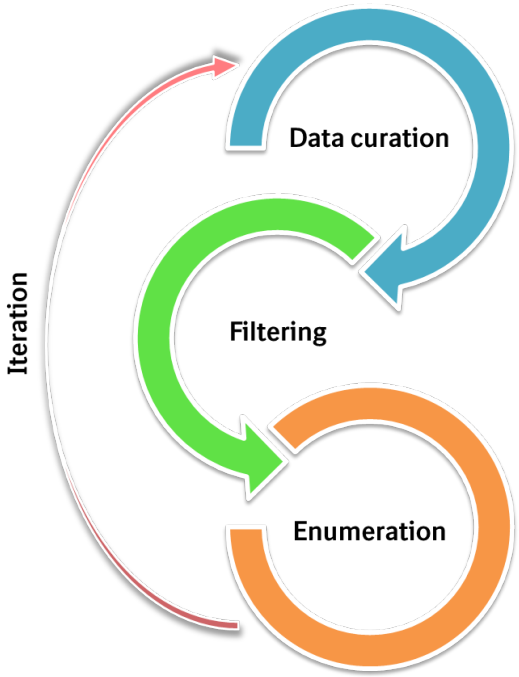
- Complete open source

4. Preliminary Results

In-depth analysis on five chemical reactions

1) 1-2-4-Oxadiazole formation

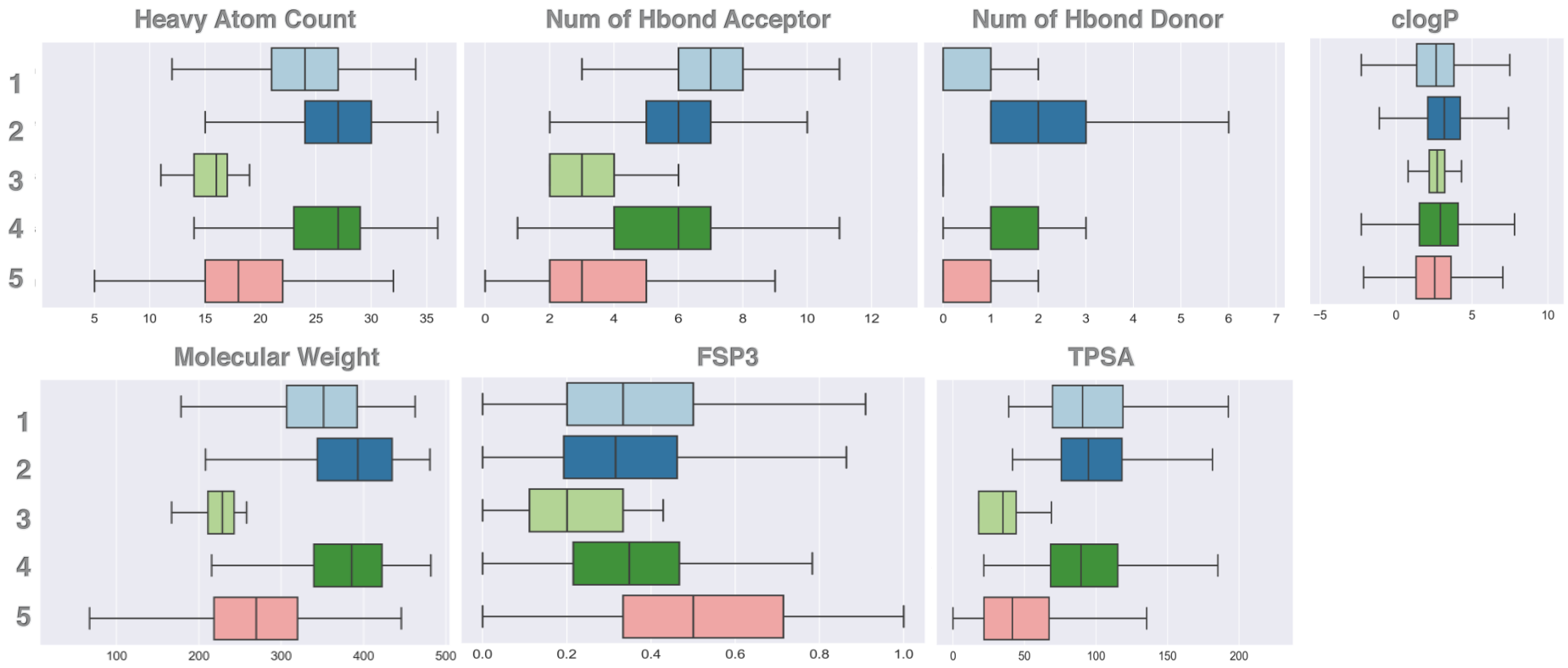




2) 1-2-4-Triazole formation from nitrile and hydrazide
3) Benzimidazole formation from 1-2-phenyldiamine
4) Friedel-Crafts acylation of heteroaromatics
5) Suzuki coupling

4. Preliminary Results

A glance at enumerated space: 100*100 reactants chosen by MaxMin diversity:



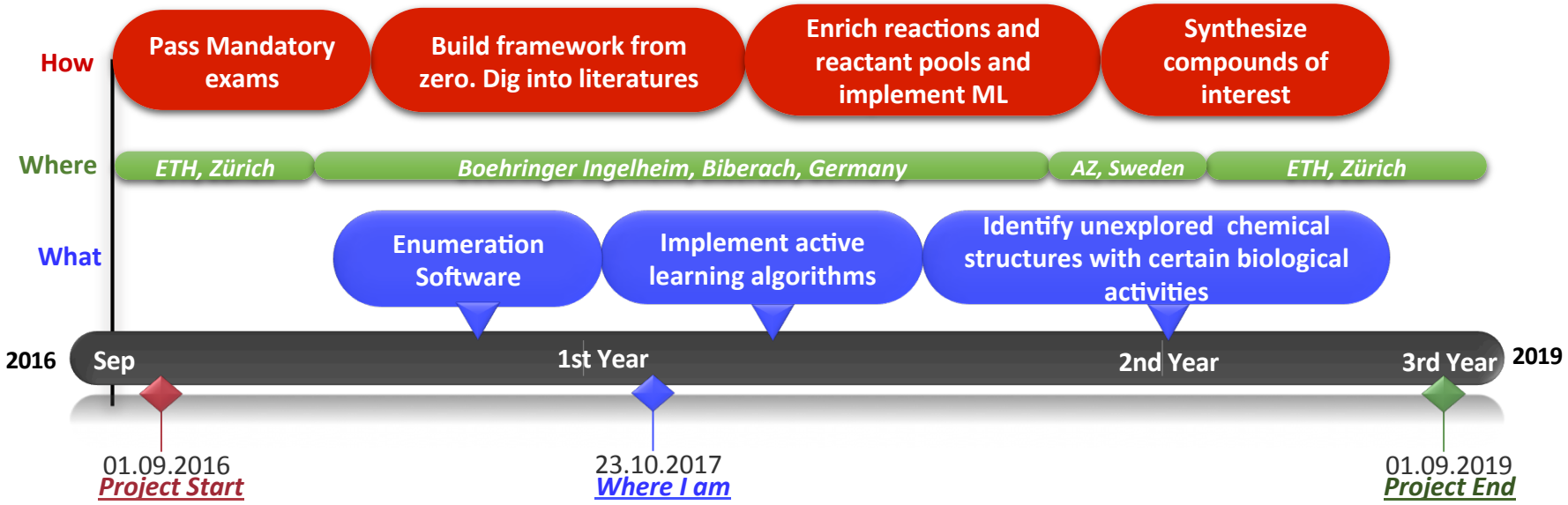
5. Conclusion and Outlook

Done:

- ***Reaction-driven enumeration software established***

Ongoing activities:

- Implementation of additional reaction-specific substructure filter
- Enrichment of reaction- and reactant-repositories
- Comparison of enumerated space with available compound collections: *e.g. DrugBank, ChEMBL*



6. Education

Research training

- BigChem weekly online courses
- 2016.09 to 2016.12, at ETH, Mandatory exams:
  - ✓ Medizinische Chemie I,
  - ✓ Therapeutic Proteins,
  - ✓ Biotransformation of Drugs and Xenobiotics.
- 2016.09 to 2016.12, at ETH, other course:
  - ✓ Computer-Assisted Drug Design
- Language course:

  two German lessons per week, since 01.2017 at Boehringer Ingelheim.
- Programming:

  two Python courses at Boehringer Ingelheim

- ETH, Lab open day, April 2017

Networking and transfer of knowledge

- GCC meeting in Mainz 05.11.-07.11.2017
- A visit & Poster Presentation at the Institute of Molecular Biology in Mainz 13.11.2017
- Poster Presentation & Discussion with other PhD & Post-Doc students on BI Science Day in Biberach (22.11.2017)

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Boehringer Ingelheim