CCP CompMedChem - Meeting Minutes (21/06/17)

Executive Summary:

A follow-up meeting to describe recent progress, outline future plans and discuss the problems of hit-to-lead in FBDD.

Four core topics were discussed. **1)** The progress since the last meeting (InnovateUK proposal and SQUONK progress) **2)** How the MD Catapult could play a role in the CCP CMC objectives **3)** What shape a proposed study weekend / hackathon should take. **4)** Best practice in hit-triaging and follow-up design for FBDD

Core outcomes:

•Trainathon/SQUONKATHON

- Who (start smaller - developers community (e.g. RDKit) and consultants), when (TBD - but probably 2017), where (a college in Oxford)
- Garrett to report back in next week or two on structured plan

•Next CCP-CMC meeting

- Andreas Bender / Andrew Leach to liaise on agenda
- Venue likely EBI, date ~October/November

•Future planning:

- Talk to UKRI / WT (these minutes are evidence)
- Build mailing list, web-presence
- Actively incorporate methods and tools of academics and use in pharma

At Cambridge (21): Anthony Bradley - Oxford / DLS; Frank von Delft - SGC / DLS; Sam Hughes - AstraZeneca; Dave Clark - Charles Rivers; Jason Cole - CCDC; Tim Dudgeon - Informatics Matters; Ben Allen - eTherapeutics; Ian Wall - GSK; Will Pitt - UCB; Andrew Leach - ChEMBL; Nathan Brown - ICR; Garrett Morris - Oxford; Steve Roughley - Vernalis; John Hancock - Earlham/Elixir; Andreas Bender - Cambridge; Brian Marsden - Oxford; Paul Emsley - Coot/CCP4; John Overington - MD Catapult; David Bailey - IOTA; Fredrik Svensson - Cambridge

Videoconference (1): Val Gillet - U of Sheffield;

Frank introduction

- Described the core-audience for CCP CMC - software developers and naive users
- Outlined the InnovateUK application - and the £1.2M project funding ~6 people over 2 years
- Overall goal - with or without this funding - is open-source self-sustaining dynamic

John Overington - MD Catapult

- Outlined MD Catapult informatics team - ~25 people in total https://md.catapult.org.uk/
- Emphasis on facilitating services (non-competitive with existing / future businesses)

Anthony and Tim - SQUONK developments

- SQUONK being actively used and appended to by XChem project

- SQUONK announced as open-source and available here: https://github.com/InformaticsMatters/squonk and https://github.com/InformaticsMatters/pipelines/

Garrett and Nathan - proposal for Workshop / Study Weekend

- Proposed training day / weekend
- Audience - chemists, structural-biologists, commercial vendors
- MDC (£10K) and Elixir both offered support / potential
- Based around SQUONK - give new open-source project a boost
- Need to discuss ground-rules for contributing to code
- Start small ~20-30 attendees

Outcomes of Roundtable

Ian Wall - GSK:

Presentation -

- Info on the whole series important
- Multi-parameter decision making on computed properties
- Decisions on where to go based on hotspot analysis
- Need for quantitative methods to guide this

Need - 1) Filter down chemistry space simply and easily. 2) Target diversity + potency
Contribution - Willing to apply anything developed on ongoing projects

David Bailey - Iota:

Need - Cell-based methods for fragments - target validation

Andreas Bender - Cambridge:

Need - A forum to evaluate methods
Contribution - Post-doc resource of novel tools into e.g. SQUONK

Dave Clark - Charles Rivers:

Need - Make the process objective and calculable
Contribution - Would be interested in trialling such a tool

Nathan Brown - ICR:

Need - Fast follow-up design, scaffold morphing
Contribution - Willing to contribute tools and methods

Steve Roughley - Vernalis:

Need - Verify NMR hits by series and capturing decisions, stop just picking winners.
Contribution - Interested in trying out new tools

Will Pitt - UCB:

Need - Hot spot analysis, strength of H-bonds and a focus on H-bonds. Evaluating H-bonding interactions. Hard to add polar groups.

Contribution - Willing to contribute advice etc

JPO - MD Catapult:

Need - Most interested in allosteric pockets, side-chain flips. Fun interfaces for chosing compounds.

Contribution - Resource for workshop / resources - if business enabling

Brian Marsden - U of Oxford:

Need - Visualisation methods for all of this - not going to design perfect method

Contribution - Post-doc in InnovateUK / addition to SQUONK

Sam Hughes - AZ:

Need - Growing then scoring. Analo

Contribution - AZ have 5 PhD students / year. A year in October could have AZ PhD on CCP CMC problem

Tim Dudgeon - Informatics Matters:

Need - Analogue generators

Contribution - Continuing SQUONK development / open-sourcing

Ben Allen - e-Therapeutics:

Need - What can you purchase.

Contribution - Can offer retrospective stats on what chemist has hypothesized vs automated methods

Andrew Leach - ChEMBL:

Need - Focus on question in mind (candidate, tool/probe, or just knowledge building. Conservative changes to start with - e.g. optimise just number of H-bonds. Start slowly - end well. We should introduce MedChem people to group

Contribution - Willing to work with us on tools. Provide EBI tools.

Fredrik Svensson - Cambridge:

Need - Communication of results and the why of results. Searching commercial space.

Jason Cole - CCDC:

Need - Ranking is bigger problem than enumerating. Is there more that xtals can tell us

Contribution - Happy to give access to software.

Garrett Morris - Oxford:

Need - Synthetically accesible space

Contribution - PhDs and post-docs and own time.