Hopping for Success
SCAFFOLD “HOPPING” WITH CONTEXT

Tyler Peryea, Rajarshi Guha, John Braisted, Noel Southall, Ajit Jadhav, Trung Nguyen

April 8, 2013
Introduction

• Scaffold is a fundamental concept in medicinal chemistry

• Scaffold-based analyses are an integral part of early stage discovery
  » Lead identification from high throughput screening (HTS) campaigns
  » Lead optimization
  » Lead “instrumentation,” i.e., addressing early stage liabilities such as IP and ADME/Tox.

• No freely available tools that meet our needs
Outline

• Overview
• Features of Scaffold Hopper
• A quick tour of Scaffold Hopper
• Future directions
Overview

• Scaffold Hopper is a freely available tool that was initially developed in-house for automated R-group analysis

• Self-contained Java webstart application running inside the Java’s secure sandbox
  » Require explicit user’s permissions for basic operations (e.g., file IO)
  » Does not transmit user’s structures over the network; communication with the server only over SSL.
  » Heavy-lifting (e.g., computing MCS) is on the client side

• Look out for additional details on our blog
  http://tripod.nih.gov

• Or take it out for a spin now
  https://tripod.nih.gov/ws/hopper/hopper.jnlp
Software features

- Automatically generate “reasonable” R-group tables for a given dataset
- Scaffold-based “clustering” of the data
- “Bird’s eye” view of the data through scaffold network visualization
- Scaffold “hopping” (in the literal sense) in the context of publications (and soon targets and assays)
- PubMed on “steroid”
  - Import data directly from PubMed ID or DOI
  - Structure searching (sub-, super-, exact, and similarity) against PubMed
  - Retrieve structures from PubMed’s text searches
Examples of scaffolds generated directly from Scaffold Hopper
A quick tour of Scaffold Hopper

Structure searching

Project generated scaffolds onto a new dataset

Text searching

Data source

Add additional custom scaffold
Quick tour (cont’d)

Entrez query syntax

Click on hyperlink to download compounds
Quick tour (cont’d)

Click on scaffold and corresponding PubMed references are downloaded automatically.
Future directions

• Integration with BARD
• Incorporate additional contexts; e.g., targets, assays, clinical trials, drugs, patents, etc.
• Explore interesting use cases, e.g.,
  » Given a set of hits from a phenotypic screen, can we identify likely targets and/or pathways?
Acknowledgements

- Deepak Bandyopadhyay (GSK)
- Min Shen (NCGC)