

# CUP 21

## ...So Where Were We?

Anthony Nicholls, CEO  
OpenEye Scientific Software, Inc.  
Santa Fe, NM  
March 8<sup>th</sup>, 2022

# What is CUP?

Florence, 14<sup>th</sup>-16<sup>th</sup> C

Giotto, Michelangelo,  
Leonardo Da Vinci,  
Botticelli, Donatello,  
(Dante, Boccaccio)



# Giorgio Vasari

*“Lives of the Most Eminent Painters, Sculptors & Architects”, 1550*



*The Adoration of the Magi*



*The Holy Family*



*Christ Carrying the Cross*



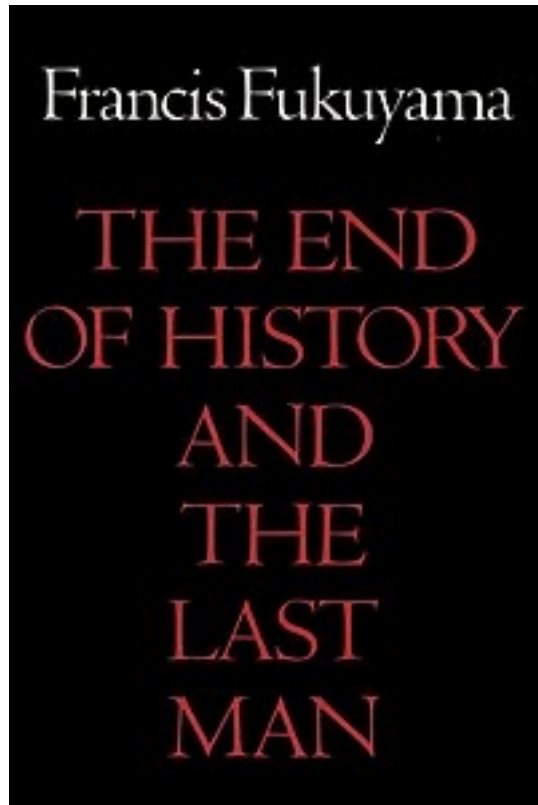
Explaining why in Florence, more than elsewhere, “men became perfect in the arts” :  
*“The spirit of criticism. The air of Florence making minds free and not content with mediocracy”*

# What is CUP?

- *“A spirit of criticism. The air of CUP making minds free and not content with mediocracy”*
- Doesn't mean we can't be (mostly) polite about it
- But be guided by the Great Bill Murray-



# In the Spirit of Criticism: Why does Francis Fukuyama still have a job?



1992

“When the Russian tanks roll westward, what defence for you and me?” – *Philip Larkin (1969)*



2022

# Avoiding WW3

- Over-reaction → World War 1
  - A singular event spiraling out of control because of a network of alliances and treaties and significant misperceptions of intent
- Under-reaction → World War II
  - A power-mad dictator with territorial ambitions being placated by countries unwilling to face the consequences of confrontation

Do we really have to ask which currently applies?

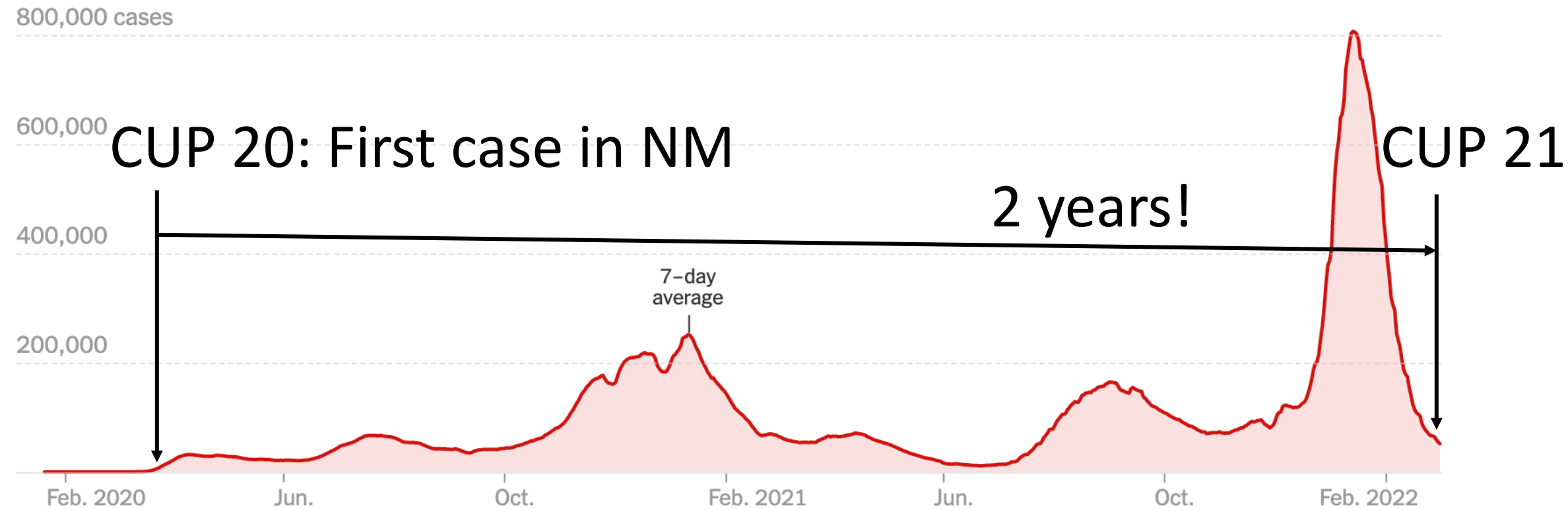


# Virtual collections in Orion



- Virtual collections based on your chemistry
  - AstraZeneca – 10B!
  - Extensive tools from OpenEye
- New vendors
  - Otava?
- Other vendors making Enamine compounds
- Any conceivable way we can help Enamine

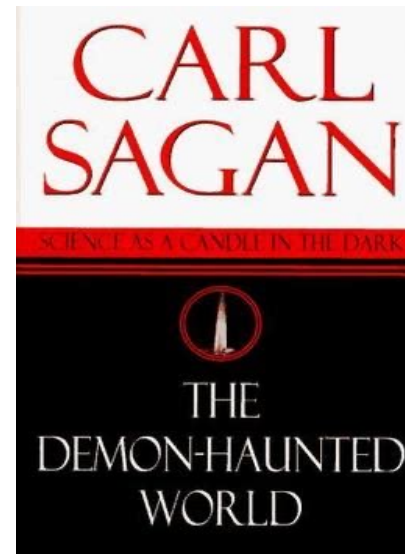
# COVID-19





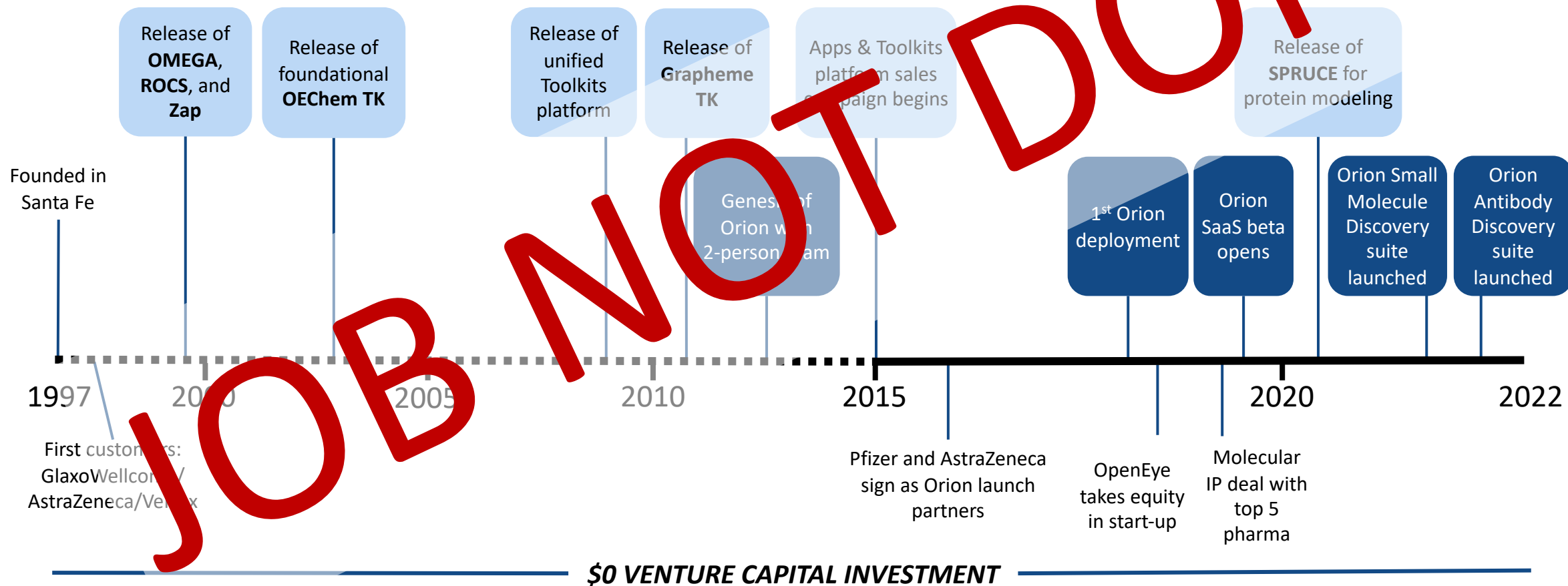
# In the Spirit of Criticism:

- Epidemiology is right up there with Economics and Psychology
- You can *only* trust the primary data and even then, not much
- Careful experiments take time.. Or human challenge!
- Rational debate was next to impossible
- Our civil society isn't

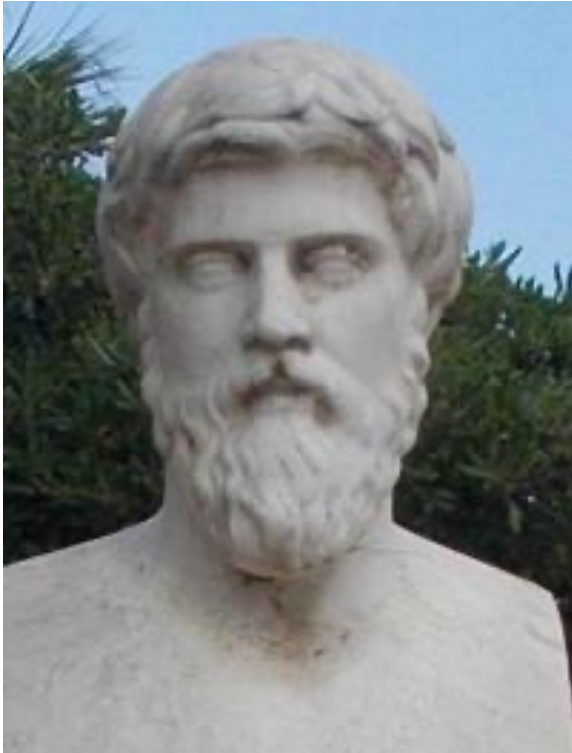


# So, Anything Else Happen? Feb 24<sup>th</sup>, 2022

## 25 Years of OpenEye



# Science



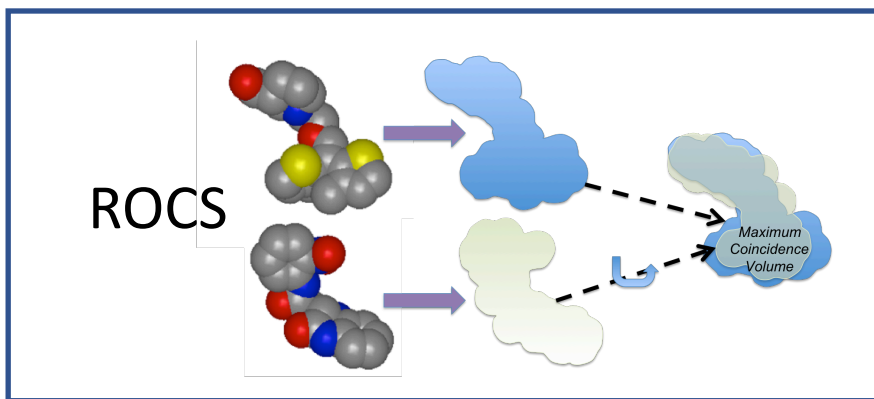
- “When Alexander saw the breadth of his domain, he wept for there were no more worlds to conquer.”

— **Plutarch**

- Shape and Electrostatics
- Orion + The Computational Revolution
- Statistics and Design

# Shape and Electrostatics

- **Shape and Electrostatics**
- Orion + The Computational Revolution
- Statistics and Design



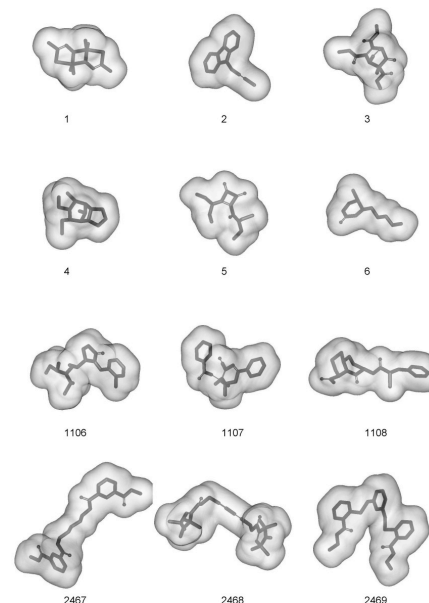
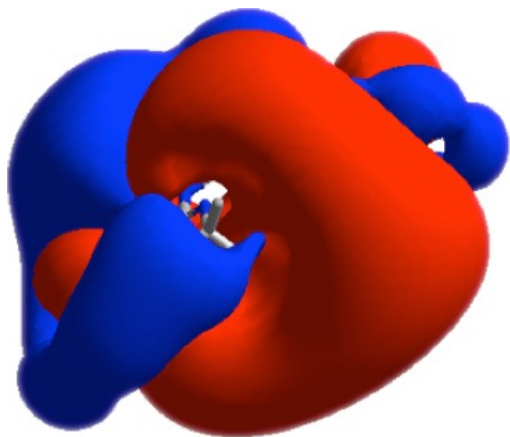
Too  
Damn  
Successful

*“Exploiting the similarity concept is a sign of immature science”.*

-Willard Van Orman Quine,



EON



Shape Space

# Back to the well

1. Can we do more with electrostatic similarity?
  - Charge similarity
  - Optimization of overlaps with electrostatics
2. Can we avoid “brute force”?
  - FastROCS
  - SubROCS
3. Can we do more with proteins?
  - Protein similarity
  - Protein-protein complementarity
4. How best to include these concepts for statistical inference?
  - Can we do better than “just” similarity?



# Orion is a Resource

- Shape and Electrostatics
- **Orion + The Computational Revolution**
- Statistics and Design



Open Source

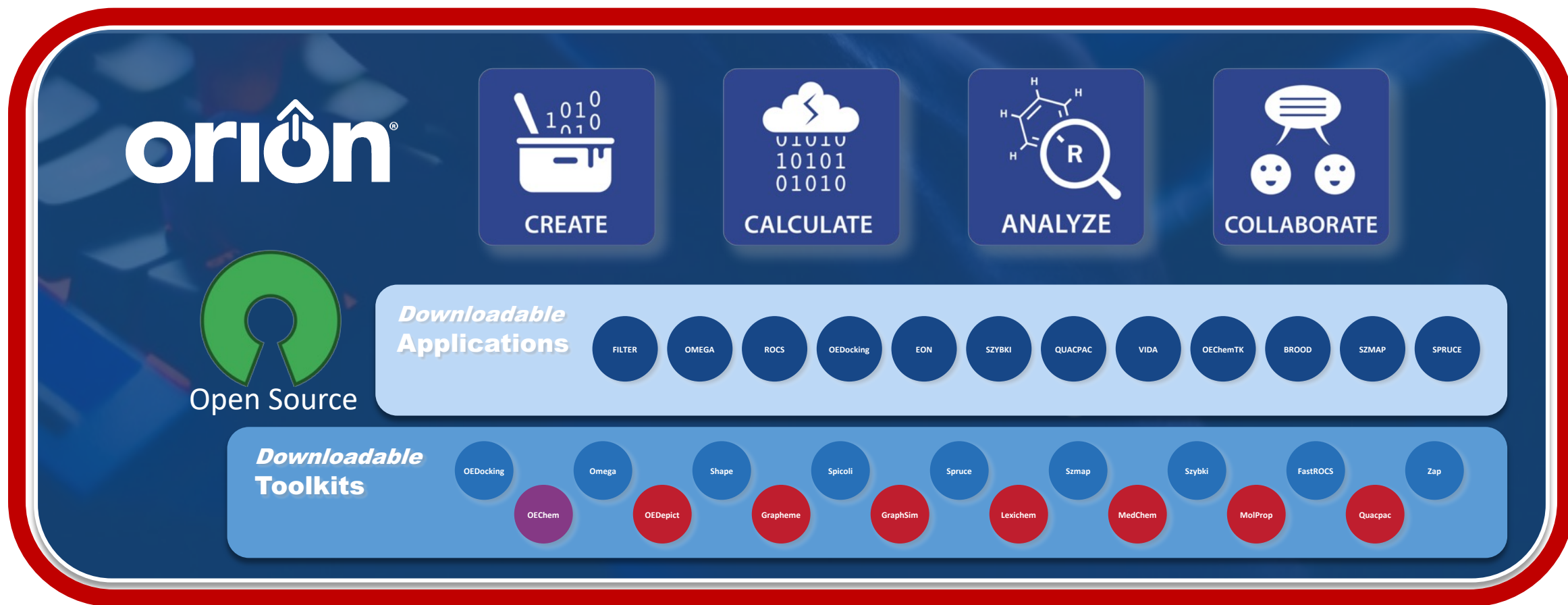
**Downloadable Applications**

FILTER OMEGA ROCS OEDocking EON SZYBKl QUACPAC VIDA OEChemTK BROOD SZMAP SPRUCE

**Downloadable Toolkits**

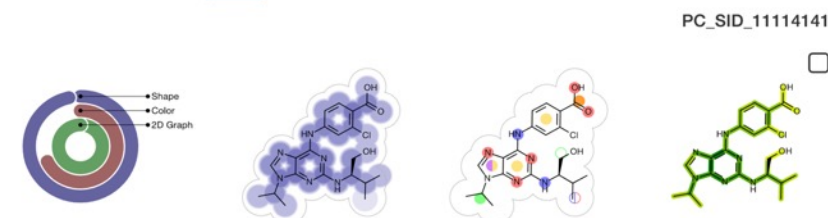
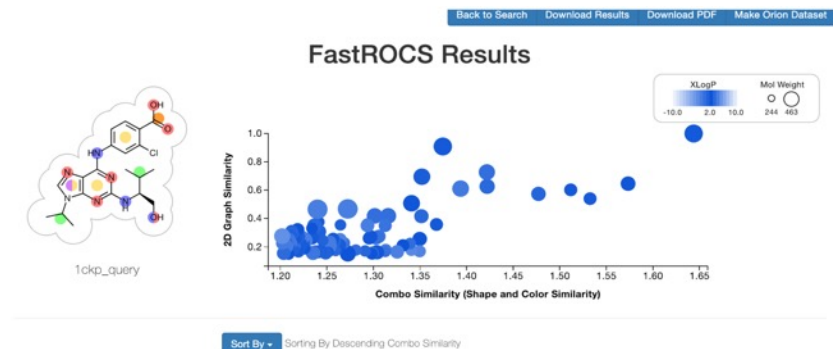
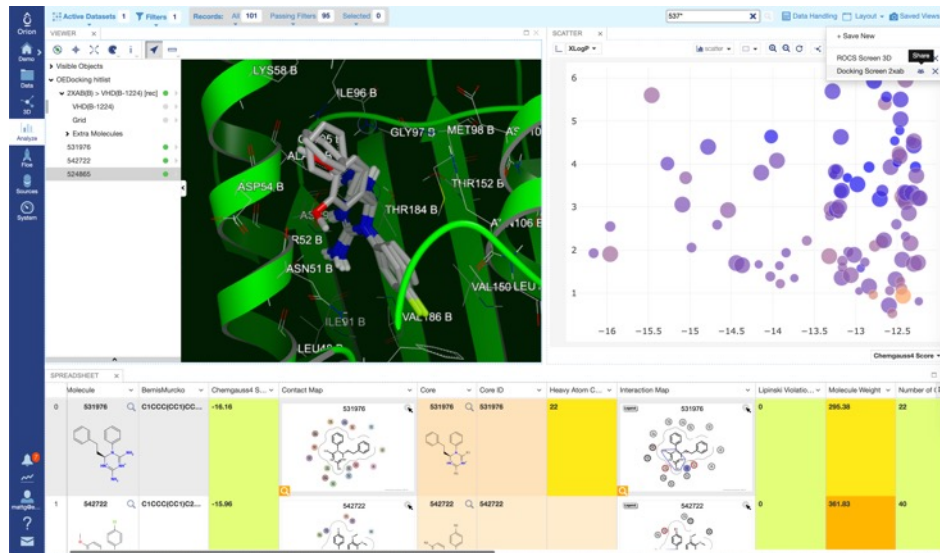
OEDocking Omega Shape Spicoli Spruce Szmap Szybki FastROCS Zap  
OEChem OEDepict Grapheme GraphSim Lexichem MedChem MolProp Quacpac

# Orion is a Destination, not just a Resource



If you had to download, we failed


Therefore, Orion needs to be a CADD Platform



Project Members


+ Add Members

Name




Matt Geballe


*you are the project owner*




☐




FolderA




Matt Bagwell




☐







3TTZB\_gameplan\_test




Kevin Schmidt




☐



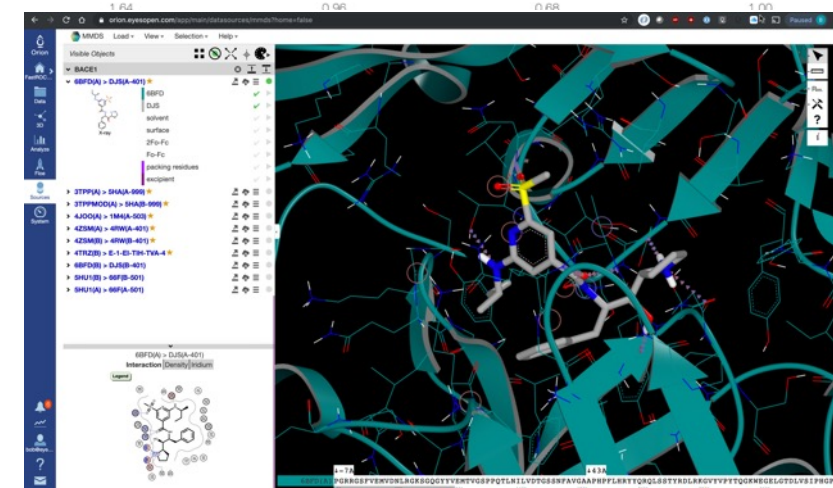


aprazolam\_freeform\_restriction\_test

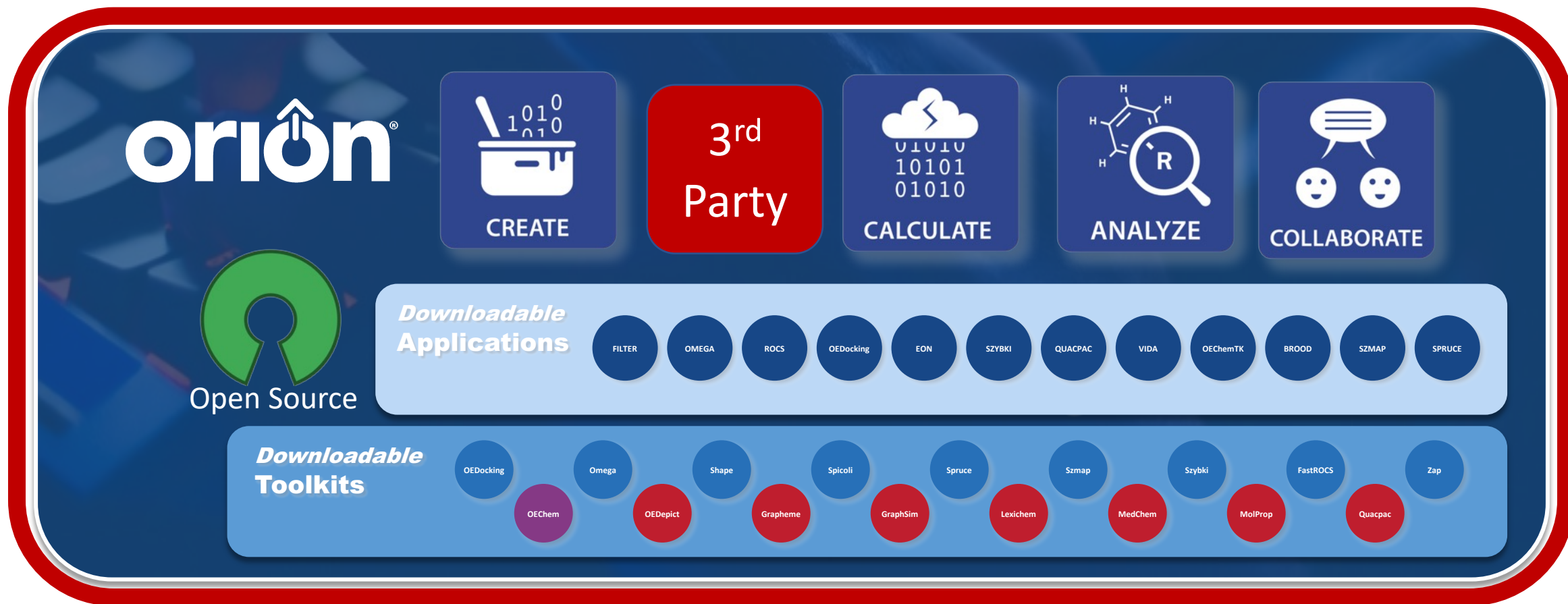
Project Data / My Data / New Site Exploration

 +

Attention needed! Please review data in your **Shared with Others** and **Collections**



# Orion is a Destination for Everyone



# OpenEye and Gaussian announce a partnership



- First time Gaussian is commercially available on the cloud
- Flores especially constructed with Gaussian code
- Help adapting your Gaussian uses to Orion
- New Orion facilities powered by Gaussian



# Cloud computational revolution



# Revolutions take time

Before



Soon After

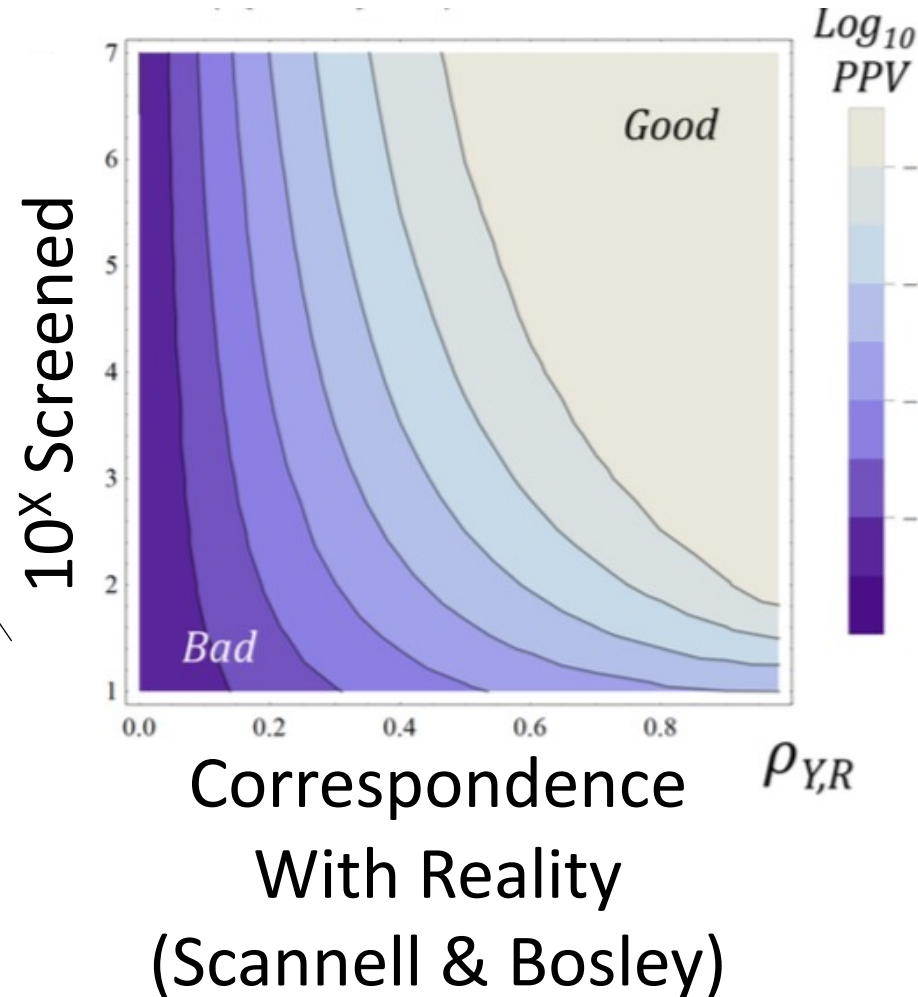


Eventually



# What you see now..

- Large-scale search
- NES - affinity
- WESTPA
  - Protein motion
  - Permeability
- CSP
  - Polymorph
  - Solubility

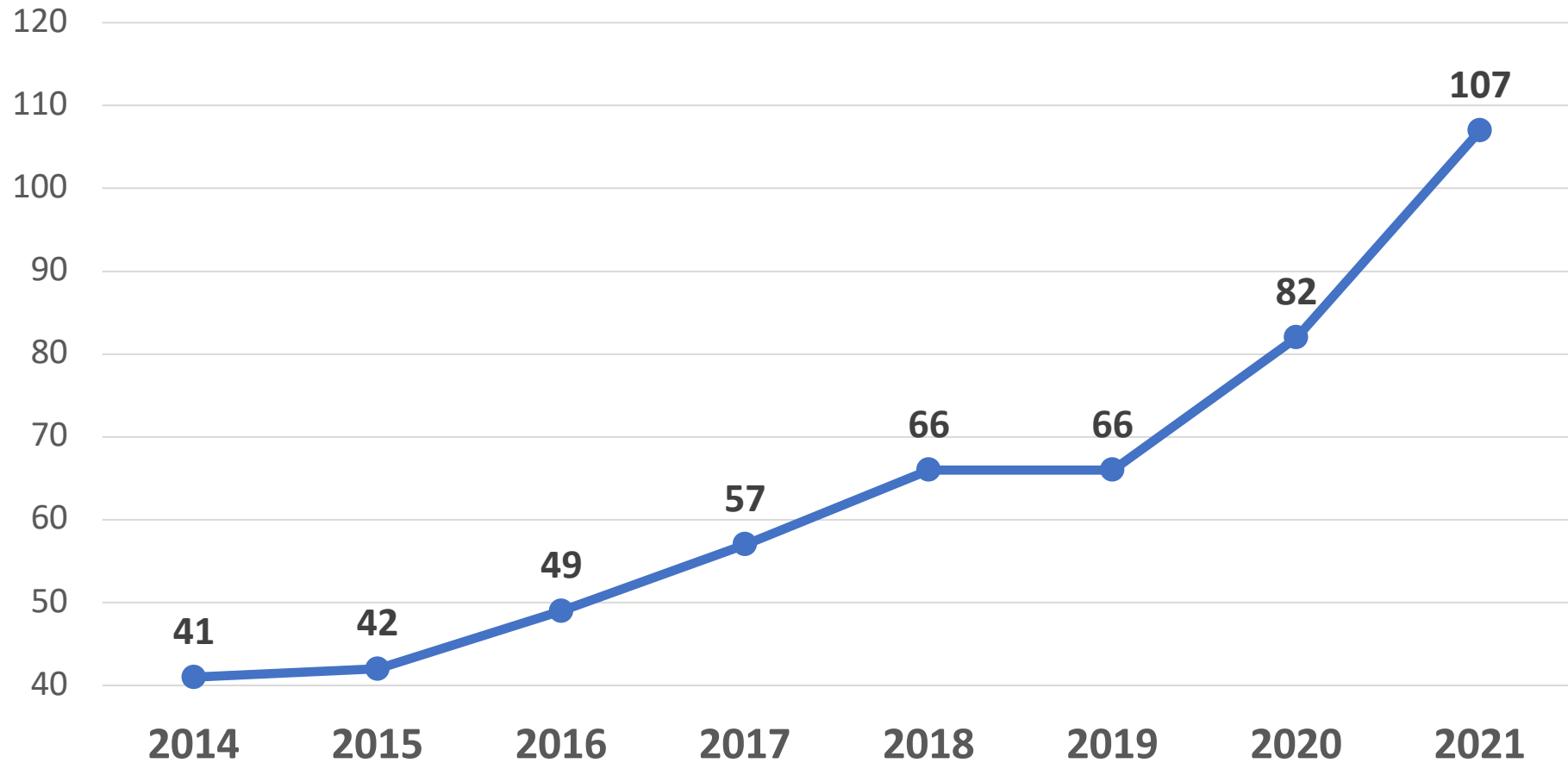


# But Cloud Computing will affect everything

PROTAC Design	Selectivity	Protein-protein interactions	Predicting chemical reactions	Off-target effects	TBD
Off-rates	Chemical Stability	Simulation of the blood-brain barrier	Catalyst Design	Stages of Metabolism	TBD
Macrocyclic Libraries	Mesoscale modeling	3-D Modeling of RNA/DNA	Biosensor Design	Dissolution Rates	TBD
Unfolded Proteins	Protein Production	Chemical Scale-up	3D Antibody Libraries	3D HTS analysis	TBD
Proteomic Analysis	PK	Cryptic Pockets	Drugability	Clinical Trial Design	TBD
TBD	TBD	TBD	TBD	TBD	TBD

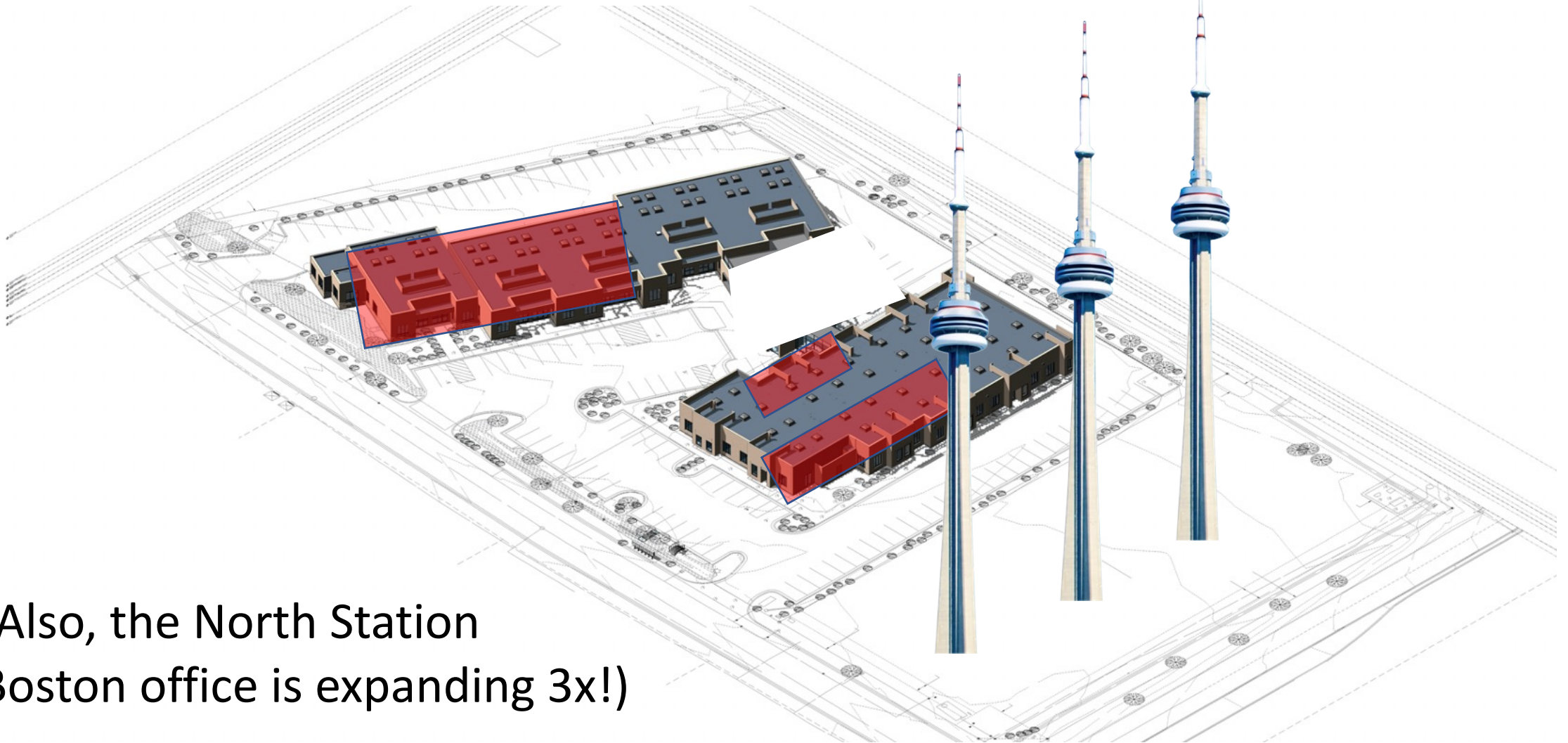
# Who's going to do all this?

OpenEye EOY Head Count





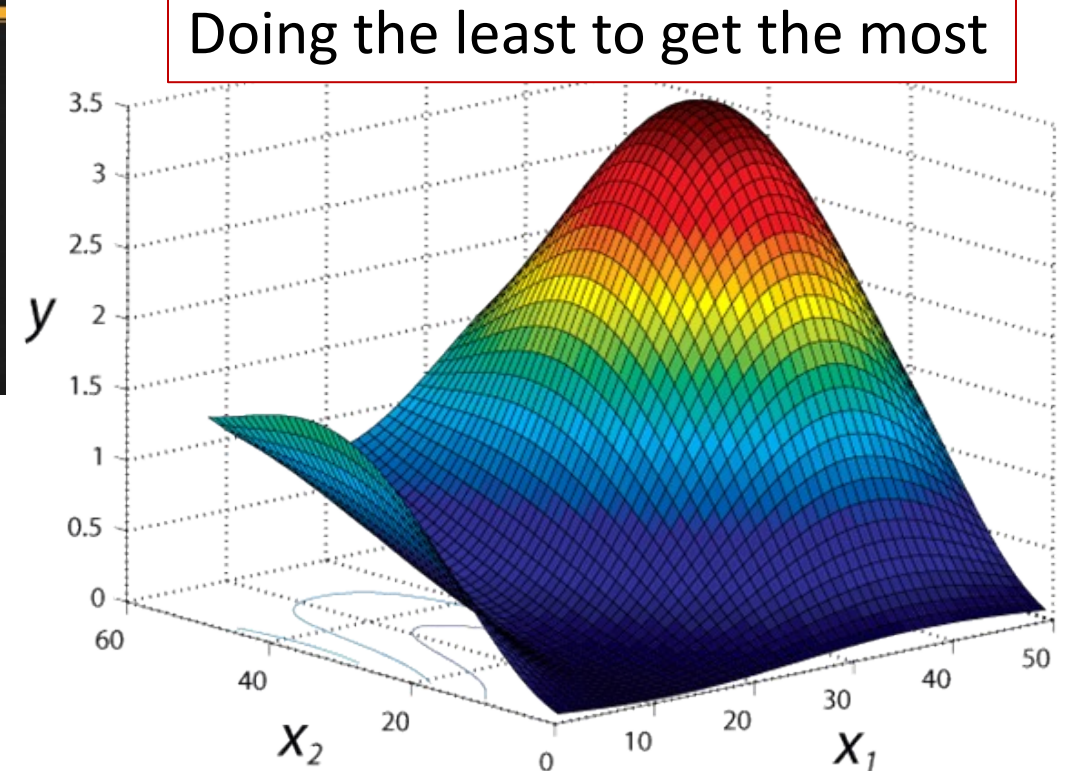
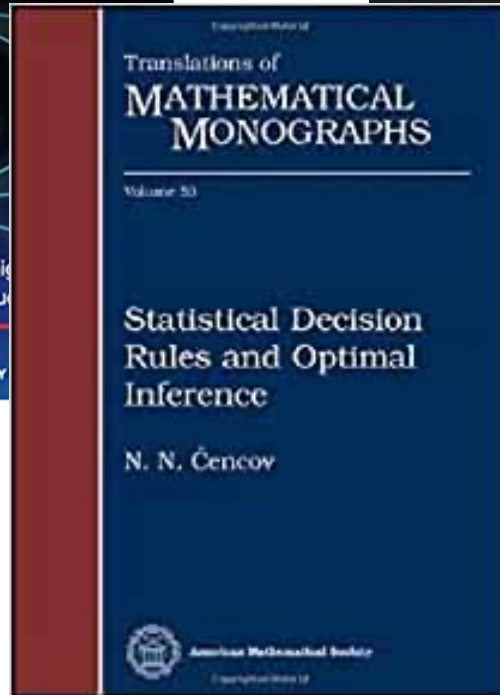
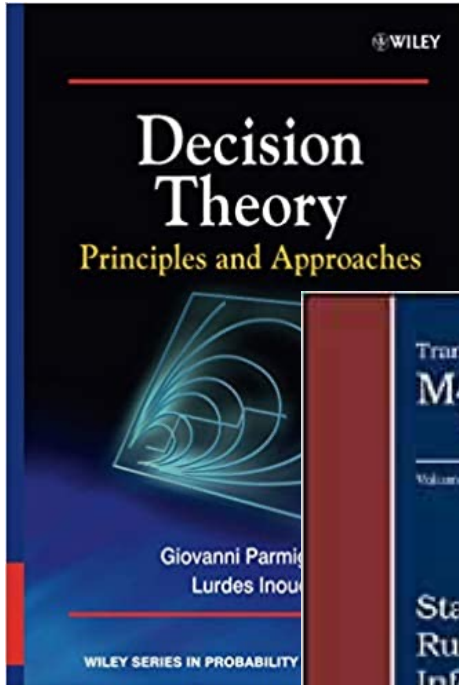
# New Office (Santa Fe)



(Also, the North Station  
Boston office is expanding 3x!)

# Statistics of Optimal Design

- Shape and Electrostatics
- Orion + The Computational Revolution
- **Statistics and Design**



# Design of Experiments

Charles Sanders Peirce  
(1839-1914)

- Logic
- Mathematics
- Statistics
- Philosophy
- Metrology
- Chemistry
- Economics
- Linguistics
- History of Science
- Experimental Psychology



“Logic will not undertake to inform you what kind of experiments you ought to make... but it will tell you how to proceed to form a plan of experimentation.

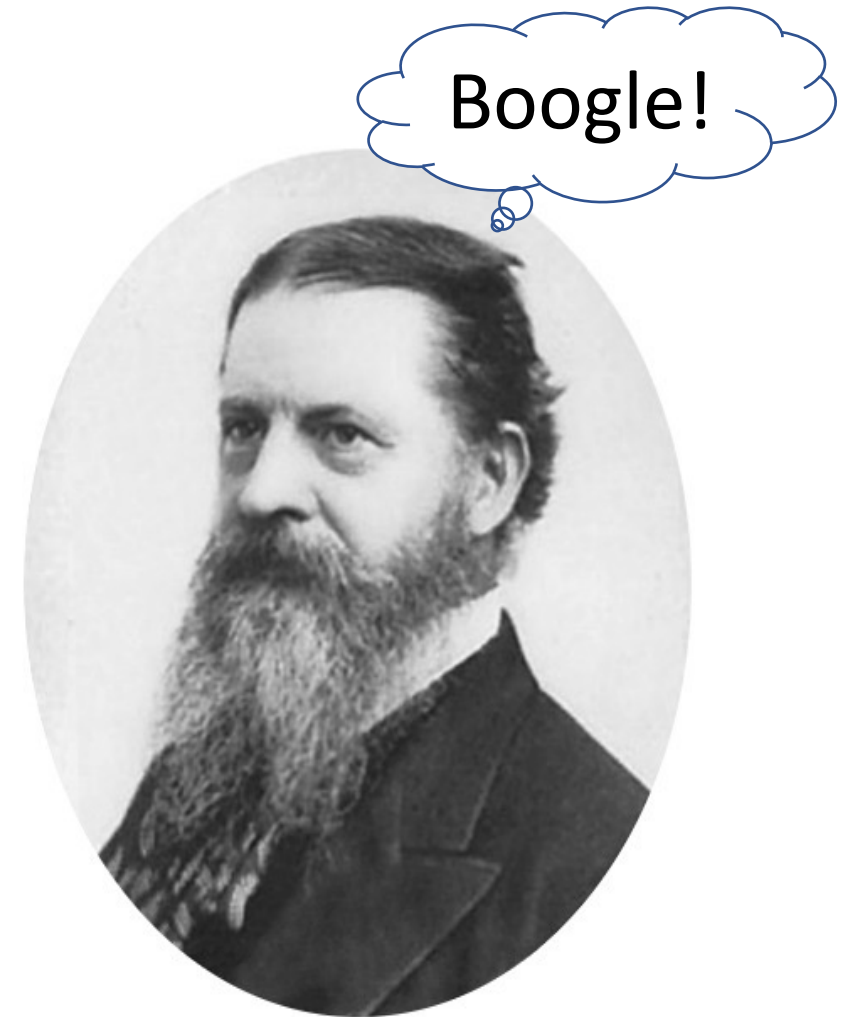
Unfortunately practice generally precedes theory, and it is the usual fate of mankind to get things done in some *boggling* way first, and find out afterward how they could have been done much more easily and perfectly.”

Talk at Johns Hopkins, 1882

# Why is DoE not used more in Drug Design?

*(GSK presentation, July 2015)*

- Seen as too abstract?
- Other factors (availability etc) over-ride?
- Lack of available software?
- Overly strong dependence of “instinct”?
- Difficulty in validating?
- Lack of appreciation?



# OpenEye Discovery Services (Announcement)

- New division, run by Bob Tolbert, **to work on the discovery process**
- Mixture of senior modeling experts, informatics developers, new hires in the mathematical arts
- Customer interactions:
  - Simple fee-for-service (Virtual Screening)
  - Partnerships on targets of interest (Hit development, Lead optimization)
  - Handing off internal projects before they run the danger of becoming candidates



# Summary

- Shape and Electrostatics: plenty of exciting science left
- Orion as a Destination and Home to the CADD Computational Revolution
- Bringing Statistical Theory to Lead Optimization
- Announcements:
  - Gaussian now on Orion
  - OpenEye Discovery Services
- After 25 years there's still so much to do

