

Introduction to CUP 22

Anthony Nicholls, CVP
OpenEye, Cadence Molecular Sciences

Santa Fe, NM

March 14th- Pi day!

2023

Welcome! You Made It!

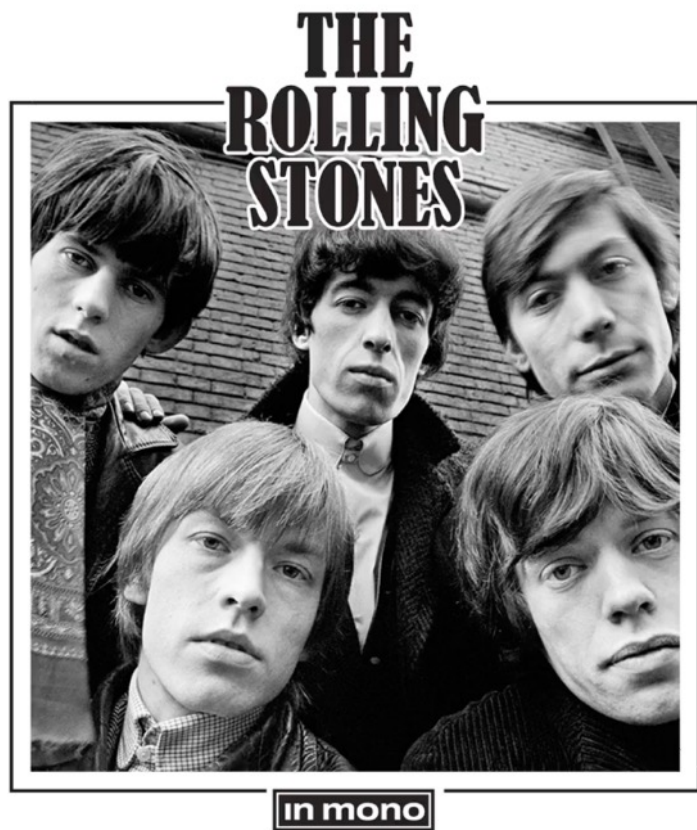


CUP Policies

- It's about the science of drug discovery
- Science requires debate
- It's considered a private meeting ... Not recorded or streamed
- Beware of the altitude (7,000 ft)
- Beware of the chile (esp. Green)
- This is a professional, not a social, event
- We are now an 'independent business unit' of Cadence Design Systems

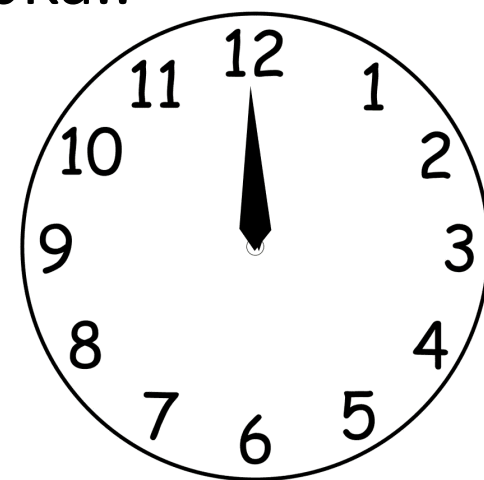
(Yes, it was an interesting year)

(Can't Get No) Satisfaction

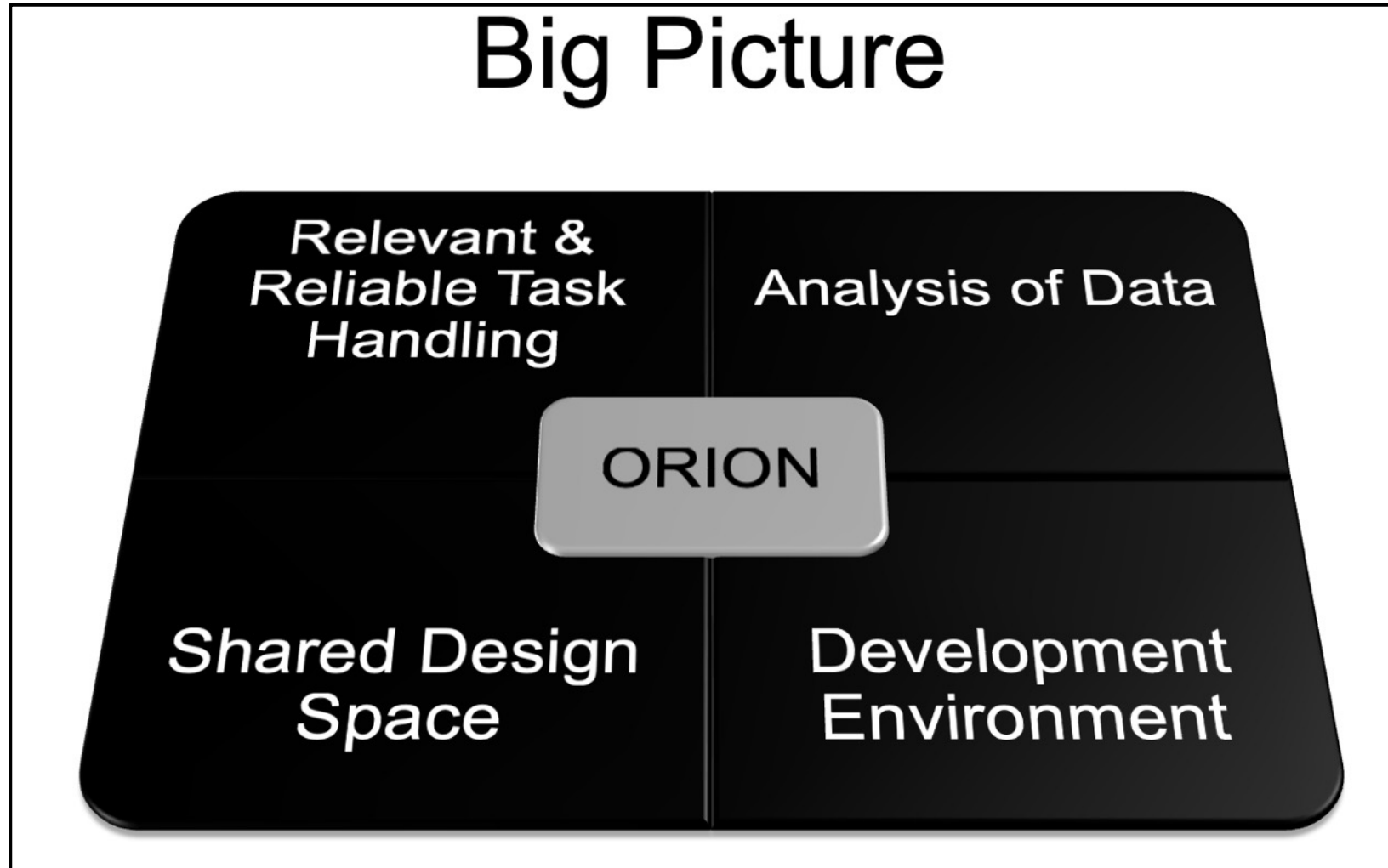


Of the many Things of which I'm not Satisfied

- Small molecule design is inefficient, we waste information
- Not much *theory* of design .. Even less for MPO
- QSAR/ML No deep, chemistry-centric, physically realistic theory
- Ditto Similarity: Mostly dumb, brute-force ways of doing things
- We don't use PB (ZAP) enough: permeability, MD, EON, pKa..
- We barely use statistics, rarely use Bayes
- "Surprisal" applied to method evaluation



And then came Orion[®]...



Slide from
April 2015
Presented at
CUP 2016

Our Concept of using the Cloud

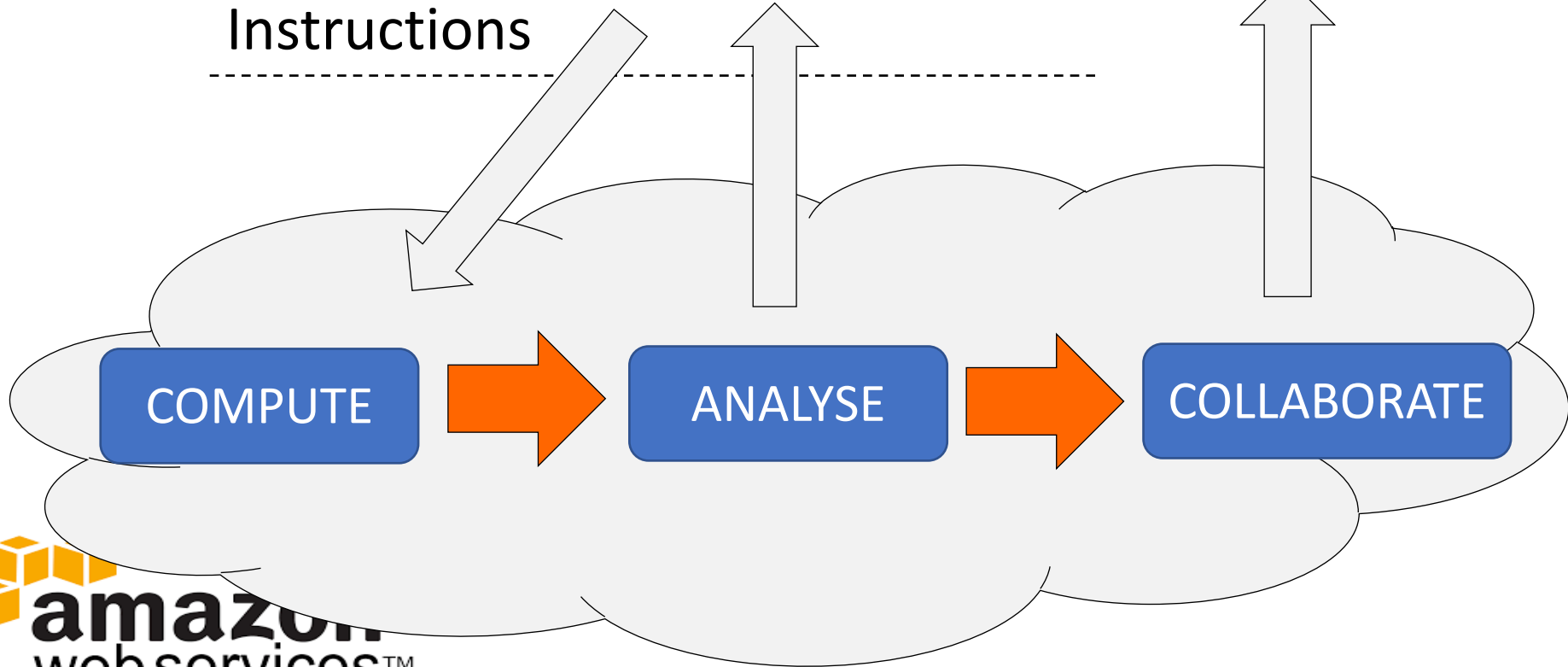
My "Andy Jassy" Slide



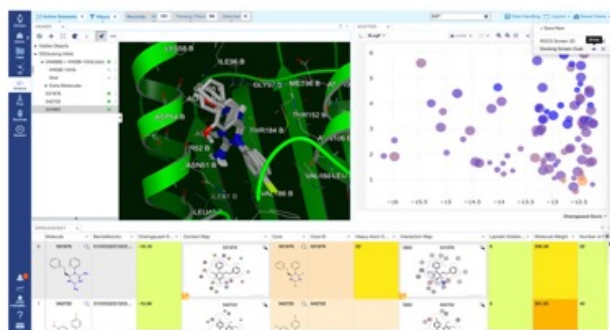
Browsing



Instructions



Already with so much new and useful Science

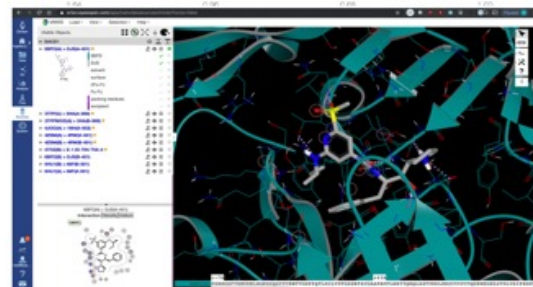


Project Members

Project Data / My Data / New Site Exploration

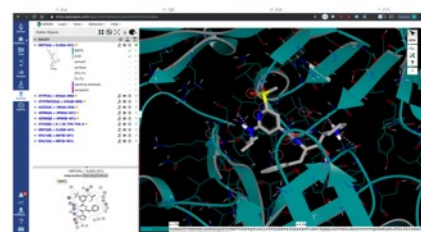
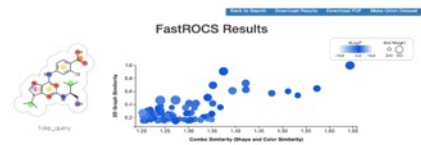
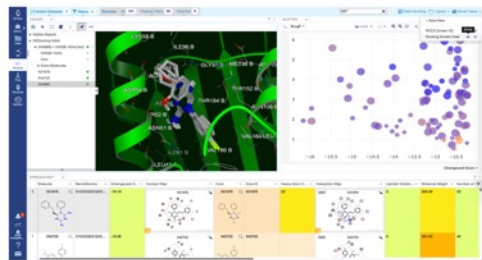
Attention needed! Please review data in your Shared with Others and Collections

Name	Role	Project
Matt Geballe	you are the project or	FolderA
Matt Bagwell		3TTZB_gameplan_test
Kevin Schmidt		aprazolam_freeform_restriction_test
		Freeform Ensemble



- Large-scale search
- Large-scale libraries
- NES - affinity
- WESTPA
- Permeability
- CSP
- AbXtract
- Gaussian

+ So much more possible!



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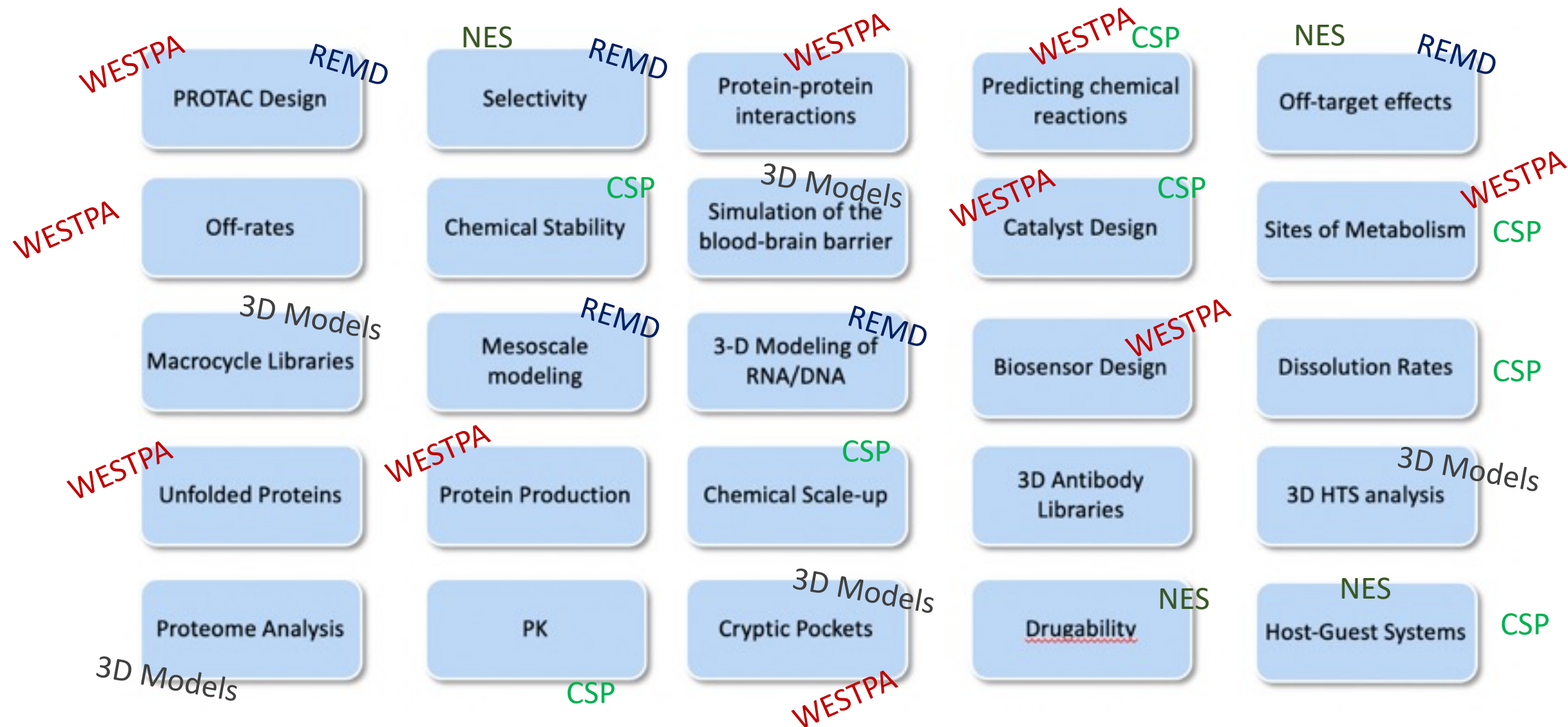
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PROTAC Design	Selectivity	Protein-protein interactions	Predicting chemical reactions	Off-target effects
Off-rates	Chemical Stability	Simulation of the blood-brain barrier	Catalyst Design	Sites of Metabolism
Macrocycle Libraries	Mesoscale modeling	3-D Modeling of RNA/DNA	Biosensor Design	Dissolution Rates
Unfolded Proteins	Protein Production	Chemical Scale-up	3D Antibody Libraries	3D HTS analysis
Proteome Analysis	PK	Cryptic Pockets	<u>Drugability</u>	Host-Guest Systems

My "blue boxes": Orion, OEToolkits, MD, QM



Not just Orion, OEToolkits, MD, QM.. Talent!

- 45 (+ 9 openings) people in Geoff's group
- They have the support of a tech team of 38 (+3 opening)
- They are using the world's best toolkits and compute environment
- They care about statistics

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- They have the support of a tech team of 38 (+3 opening)
- They are using the world's best toolkits and compute environment
- They know about statistics
- We have a history of successful collaborations:
 - ZAP, ROCS[®], AFITT, POSIT, FastROCS[™], Orion
- We currently have industry collaborations on :
 - Cryptic pockets, CryoEM, Larger Scale Search, QSAR, MD

We have the tools, we have the talent, but...

“No bucks, no Buck Rogers”



Strategic Interests

Complement

Simulations

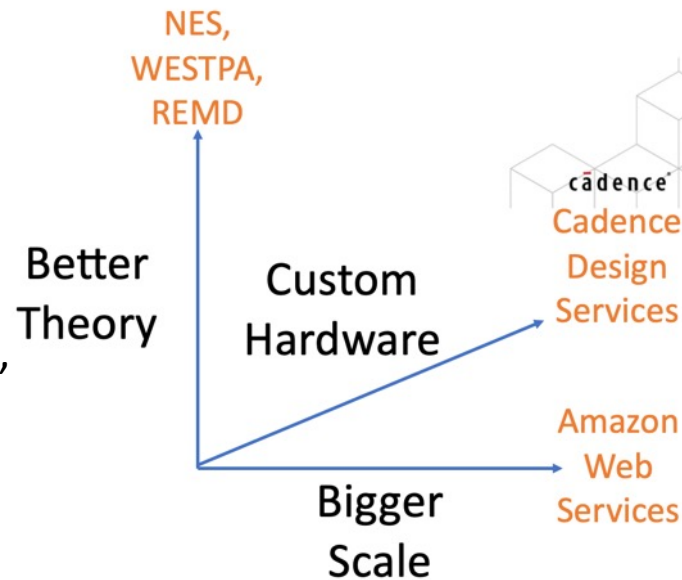
Asset

Private Equity

- Vista Equity Partners
- OrbiMed
- BASE Investment Corp
- Vista Point Advisors
- Redwood Growth Partners
- Arrowroot Capital
- Kester Capital
- Valsoft Corp
- Summit Partners
- Resolve Growth Partners
- Cove Hill Partners
- Century Equity Partners
- Battery Ventures
- Susquehanna Growth Equity
- Landmark Ventures
- Vitruvian Partners
- Queen’s Park Equity
- Bain Capital
- KKR
- Warburg Pincus
- Sageview Capital
- Denali Growth Partners
- TTM Capital
- Aldrich Capital
- JMI Equity
- ClearThink Capital
- C6 Capital
- Level Equity
- Bregal Sagemount
- K1 Capital
- Accel-KKR
- Banyan
- Housatonic Partners
- Prime Capital

So, what did we see in Cadence?

- Leadership
- Friendliness
- Belief in Science & Software
- Long-term willingness
- Tech talent
- Hardware
 - Alan Kay, “People who are really serious about software should make their own hardware.”



“We like you because you do not compete with your customers. We sell software to help people design things they want to make”



Anirudh Devgan
CEO of Cadence

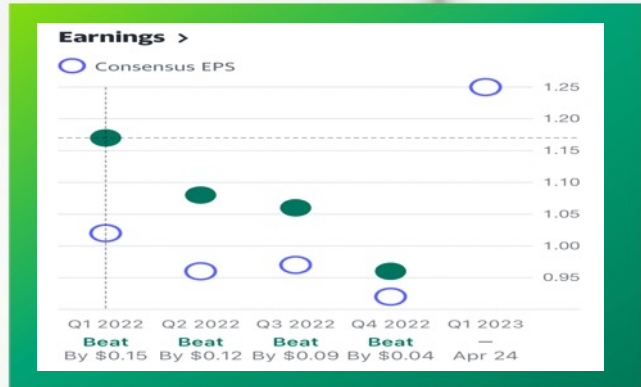
They are also a Powerhouse

Leading provider of **Intelligent System Design™ solutions**— software, hardware, and IP that turn design concepts into reality



Computational software
for designing today's electronic systems

EBITDA: 1.2B on 3.5B in sales
Full Time Employees: **10,200**
HQ: San Jose, CA



23
Global development centers

Software subscription model

Very high customer renewal rates and loyalty

Nasdaq: CDNS; S&P 500 and Nasdaq 100 indexes



So how has it gone? Is it Bittersweet?

- Closed the deal August 31st, 2022
- Most integration issues solved by patient discussion and goodwill
- No one has left
- Funding some projects – but not all
- Still rapidly hiring and growing –
 - **TOTAL FTE Open positions= 26**
 - **14 internships**
- It hasn't been bitter at all

Recap:

Offered a great price

Liked the company, the people, their approach

Selectivity : A Sad Story

- Company X invited us to look at some problem projects
- Target was a protein with isoforms identical in the active site
- No traditional SBDD way to design in selectivity
- Obvious solution (suggested):
 - Use Orion + OEToolkits (+ NES) to find *dynamical* differences
 - Design to *those* differences
 - Suggestion not embraced, despite Company X having all the tools
- (Independently) Relay followed that strategy and have a highly selective compounds in the clinic

Is this (now) a field without Ambition?

- Has this become just a “turn-the-crank” discipline?
- Drug industry new “modalities” hardly suggest this:
 - Biologics, PROTAC/ Glues, CAR-T, I-O, RNA Vaccines, CRISPR...
- Or is Machine Learning just the easy (=lazy) answer to everything?
- Or are we not providing you enough evidence of what’s possible?
- What PoC do you need to get on-board?

On-board = Feature Acceleration Agreements

- Area of mutual interest
- 2- or 3-year agreements
- Pay to prioritize our research/ grow a team in the OpenEye milieu
- Milestones. Or not. Backend payments. Or not.
- You get first access to the tools
- Have them specifically designed to solve your problems.
- Eventually shared with everyone else.. Enrich the “Commons”
- Let's go!!

Last thoughts on Ambition

- Ah, but a man's reach should exceed his grasp... *Robert Browning*

Last thoughts on Ambition

- Ah, but a man's REACH should exceed his GRASP... *Robert Browning*

Last thoughts on Ambition

- Ah, but a man's reach should exceed his grasp... *Robert Browning*
- The aim, if reached or not, makes great the life: Try to be Shakespeare, leave the rest to fate!... *Robert Browning*
- You can't always get what you want, but if you try sometimes, you just might find you get what you need... *Mick Jagger*

Enjoy CUP!