

Computer Aided Drug Discovery: Fishing in the Virtual Flood of *in silico* Data

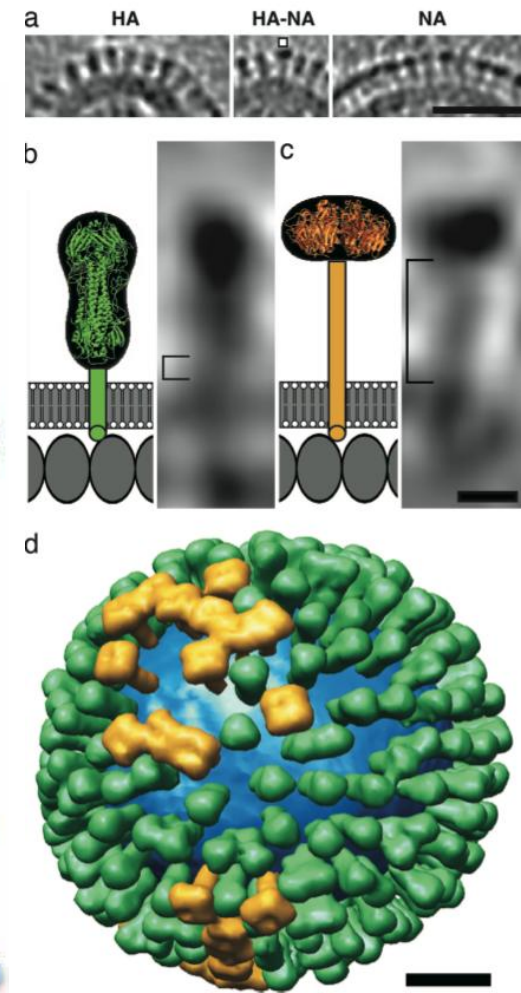
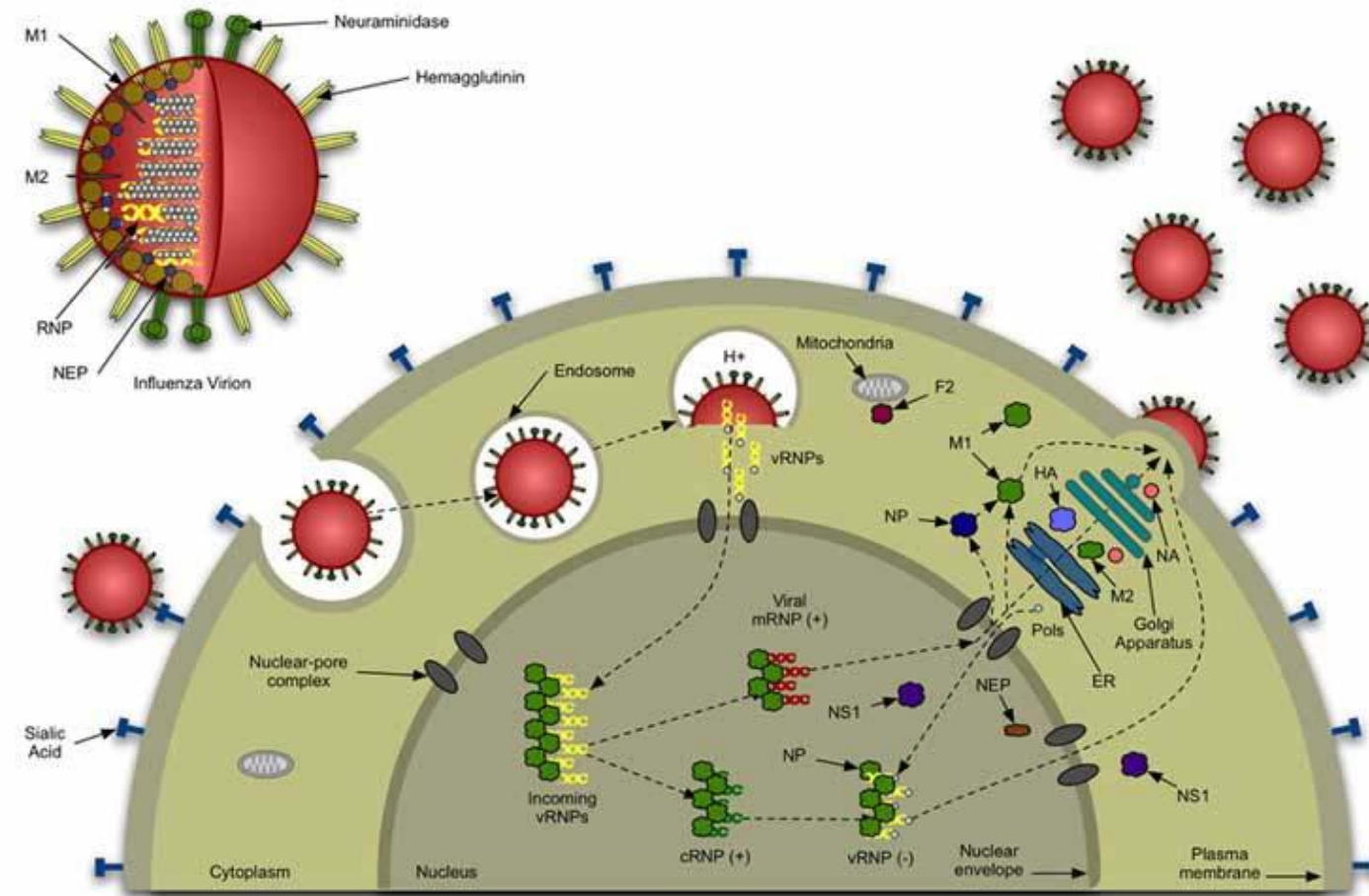
Wilfred W. Li, Ph.D.

SEAIP 2010

蕙荪林场, Dec 9, 2010

National Biomedical Computation Resource
CRBS, CALIT2
San Diego Supercomputer Center
University of California, San Diego

Viral Replication Life Cycle

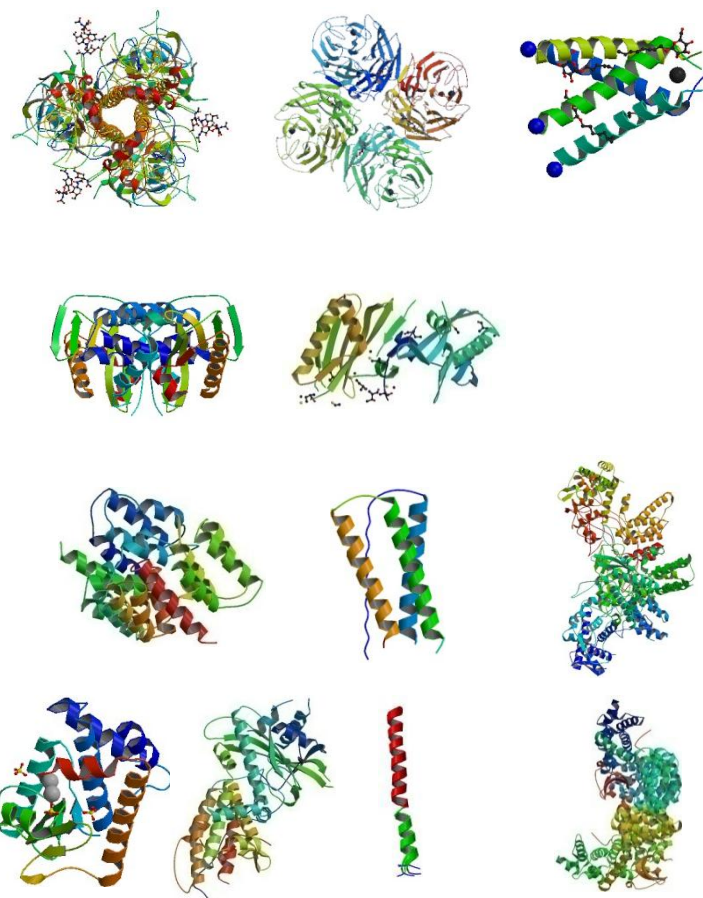


Harris et al, PNAS, 2006

<http://www.reactome.org/>
<http://www.wikipedia.org>
<http://library.thinkquest.org/05aug/01479/prevention1.html>

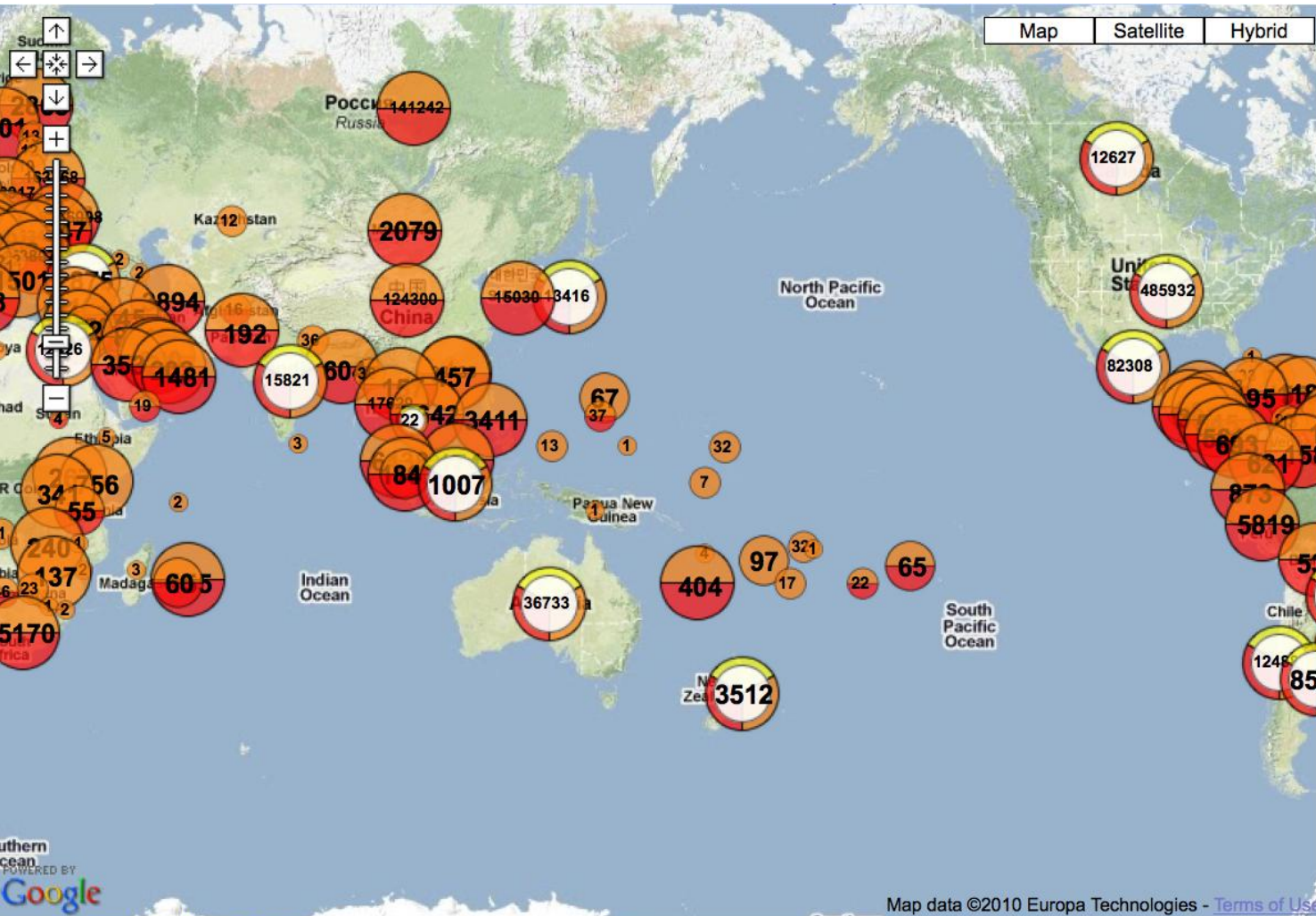
Influenza proteome and crystallome

Protein	Selected known functions	Crystal structural or NMR info	PDB ID and References
HA (Hemagglutinin)	Glycan receptor binding, membrane fusion	H5 trimeric complex	H5: 2FK0 ⁷ ; 2IBX ¹⁹ ;
NA (Neuraminidase)	Cleavage of SIA terminal residue, release of viral particles	N1 tetrameric complex	N1: 2HTY, 2HU0 ⁶ ;
M2 (proton channel)	Uncoating of viral envelope in endosome	NMR or crystal structure of transmembrane domain in complex with amantadine	M2 transmembrane domain: 2RLF ⁸ ; 3BKD ²⁰
NS1 (Nonstructural protein 1)	Host immune response modulation	RNA binding domain (RBD) and effector domain (ED) crystallized separately or in complex	NS1 RBD: 1AIL ²¹ ; NS1 ED: 2GX9, ²² H5N1 NS1: 3F5T ²³
M1 (matrix protein)	Formation of ribonucleoprotein complexes with viral RNA	Two domains separated by linker region	M1 N-terminal domain: 1AA7 ²⁴
NS2, NEP (Nonstructural protein 2, nuclear export protein)	Nuclear export of viral ribonucleoproteins	ED available	NS2 ED: 1PD3 ²⁵ ,
NP (nucleoprotein)	Formation of viral capsid and packaging of RNA	Full length	NP: 2IQH ²⁶
PA (acidic protein)	Endonuclease and cap snatching	N-terminal domain; C-terminal domain bound to PB2	PA N-terminal domain: 2W69 ²⁷ , PA C-terminal domain: 2ZNL ²⁸
PB1 (basic protein 1)	Polymerase catalytic subunit	In complex with PA	PB1 N-terminal domain: 2ZNL ²⁸
PB1-F2 (basic protein 1 frame 2)	Pro-apoptosis	NMR structure	PB1-F2: 2HN8 ²⁹
PB2 (basic protein 2)	Nuclear import of RNA; capped RNA recognition	NMR and crystal structure in complex with importin	PB2 C-terminal domain: 2JDQ ⁹ ; 3CW4 ³⁰



<http://www.pdb.org>

2009 H1N1 Pandemic Influenza



- Cumulative cases represented in Google Map as of 21 Apr, 2010
- WHO: 18769 deaths to date
- US: 4642 deaths; 480230 total cases
- Malaysia: 74 deaths, 6463 total cases
- China: 650 deaths; 124300 total cases
- Postpandemic period as of Aug 2010
- 0.5~1% death rate, similar to seasonal flu
- Targets younger and healthy individuals, different from seasonal flu (90% > 65 years older)

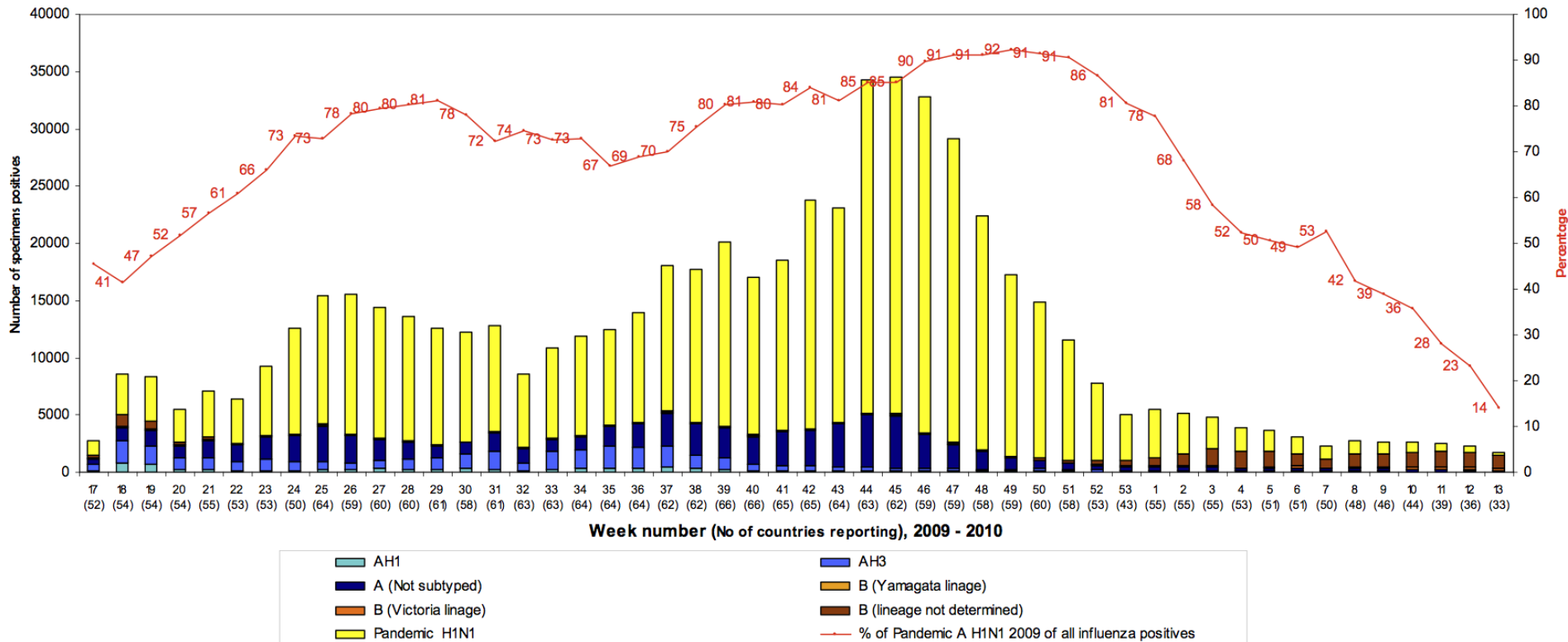
● Suspected (9029)
● Confirmed/Probable (8753967)
● Fatal (14346)
● Suspected & Confirmed/Probable
● Suspected & Fatal
● Confirmed/Probable & Fatal
● Suspected, Confirmed/Probable & Fatal

Circle size relative to number of cases. Zoom for more detail.

Source: <http://flutracker.rhizalabs.com/>

WHO Status Update

Week 17 (Apr 19, 2009) to Week 13 (Apr 3, 2010)



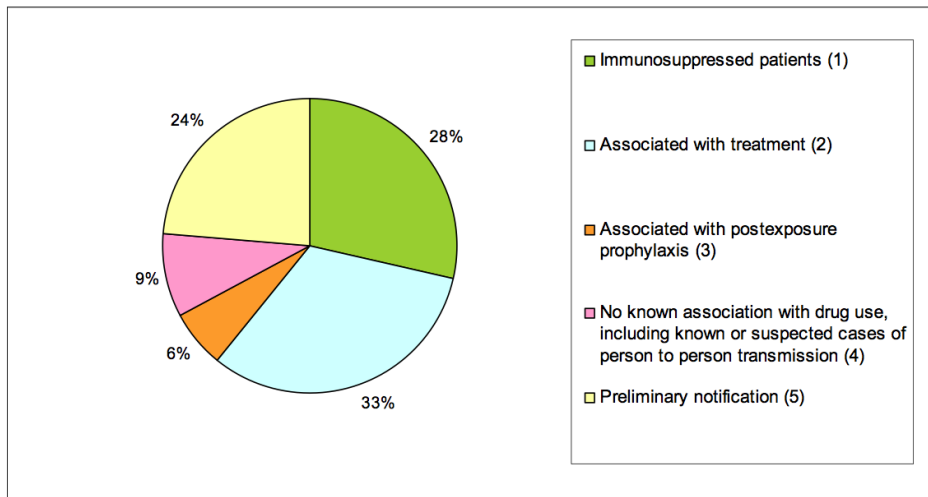
http://www.who.int/csr/disease/swineflu/laboratory23_04_2010/en/index.html

Oseltamivir (Tamiflu) Resistance in 2009 H1N1 pandemic virus

Table 1: Geographical distribution of oseltamivir resistance by the WHO regions (as of 04 August 2010)

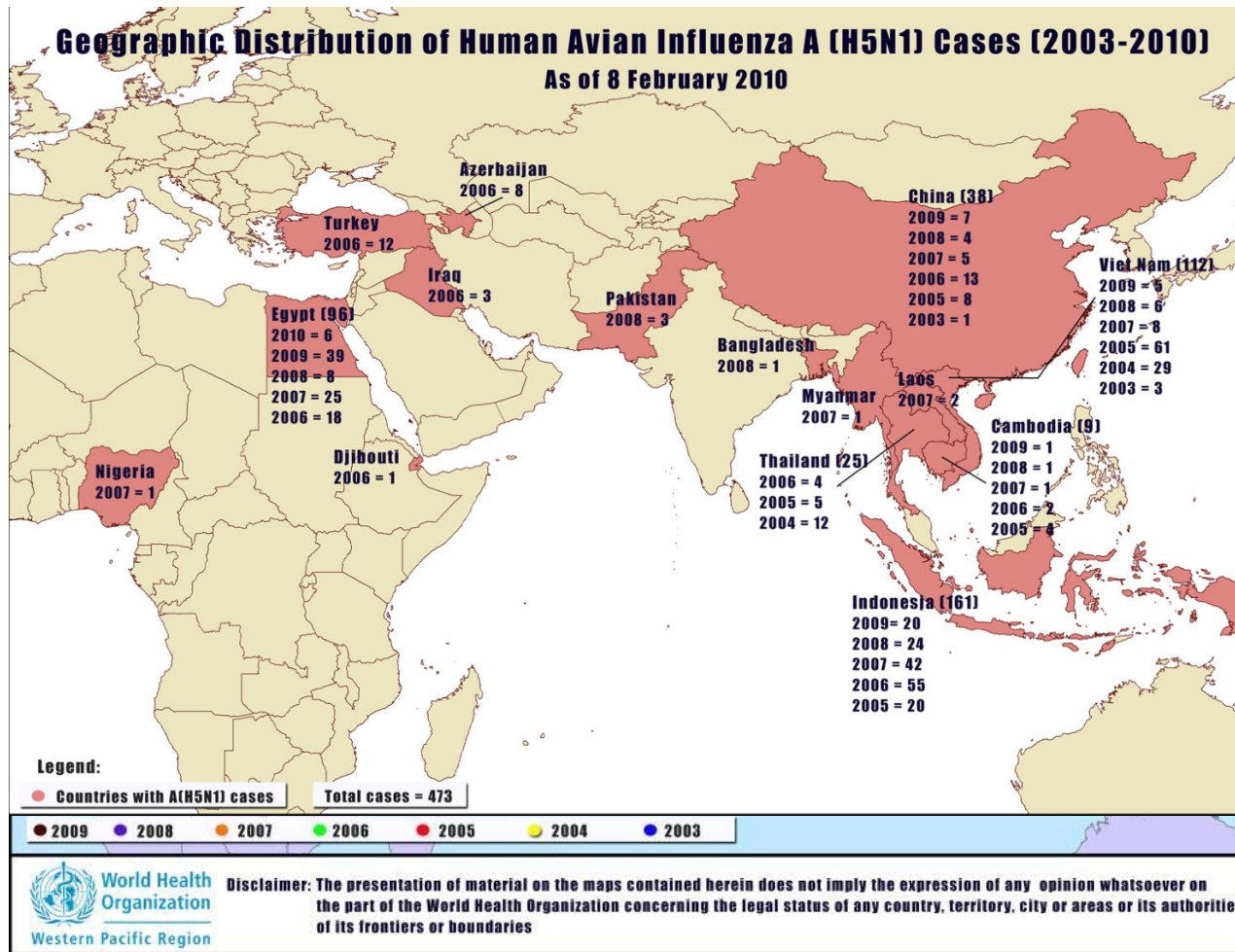
	WHO Region					
	AFRO	EMRO	EURO	PAHO	SEARO	WPRO
Number of oseltamivir resistant isolates	0	1	99	82	0	120

AFRO (Africa), AMRO (Americas), EMRO (Eastern Mediterranean), EURO (Europe), SEARO (South-East Asia) and WPRO (Western Pacific)



<http://www.who.int/csr/disease/swineflu/oseltamivirresistant20100806.pdf>

Reported human cases of avian influenza (H5N1) infection

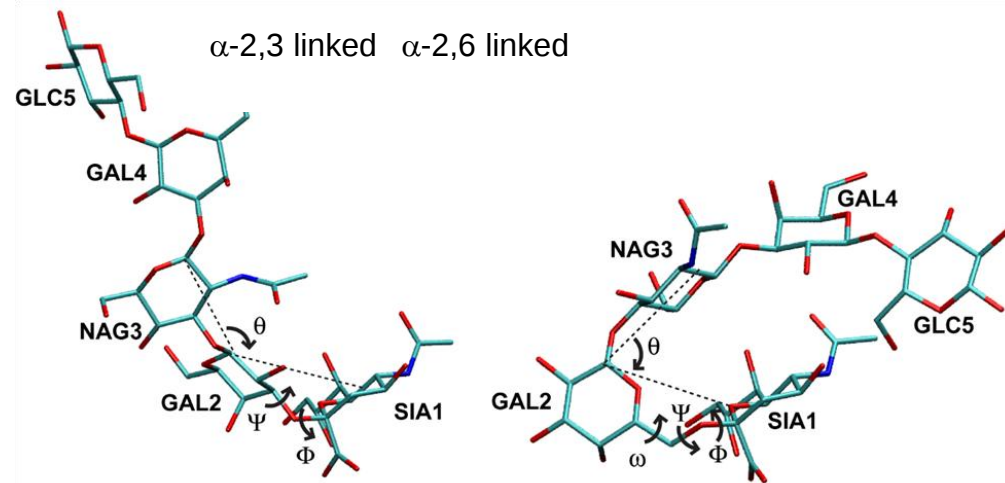
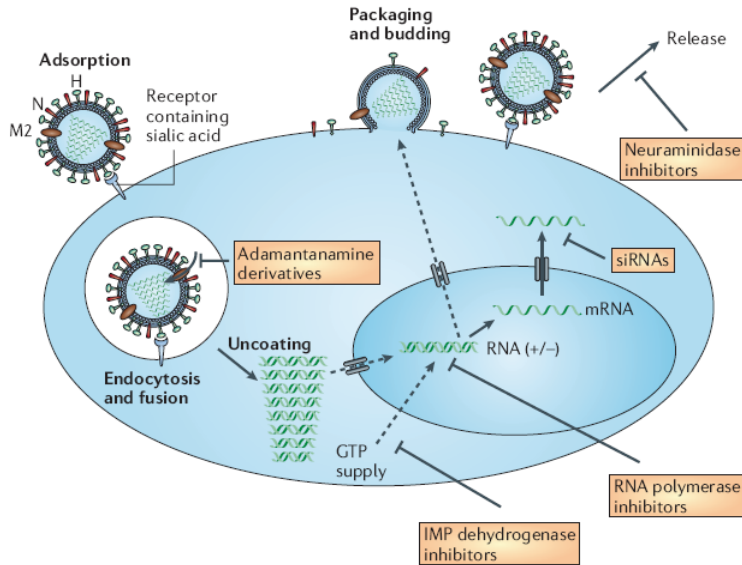


- 6 countries with continuous cases totals 356 Egypt reported 6 cases in 2010
- 15 countries with 412471 cases to date; 282 deaths
- Age ranged 3 months to 81 yr, 90% <39 yr
- Death rate varies by country, average of 63%, highest 83% (Indonesia)
- People 10-19 years affected most; people > 50yr least affected.
- Gender neutral

http://www.wpro.who.int/sites/csr/data/data_Maps.htm

Jan-13, 2009-Feb 2, 2010 statistics

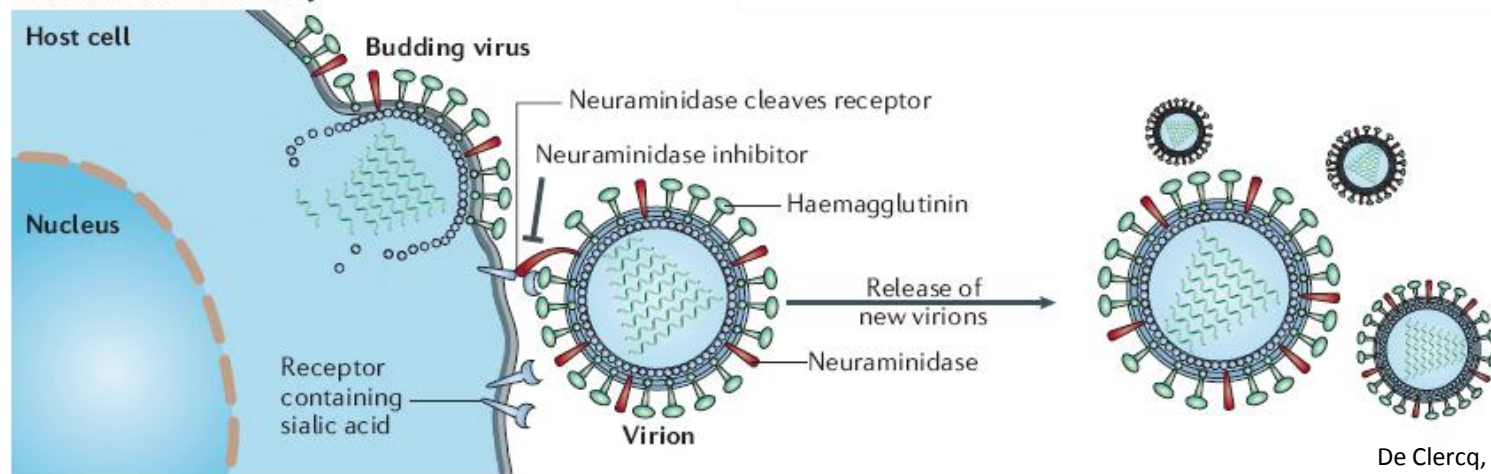
Points of Intervention in Viral Infectious Cycle



HA Binds to naturally occurring glycan receptors

Xu et al, JMB, 2009

a Neuraminidase activity



De Clercq, Nat Rev, 2006

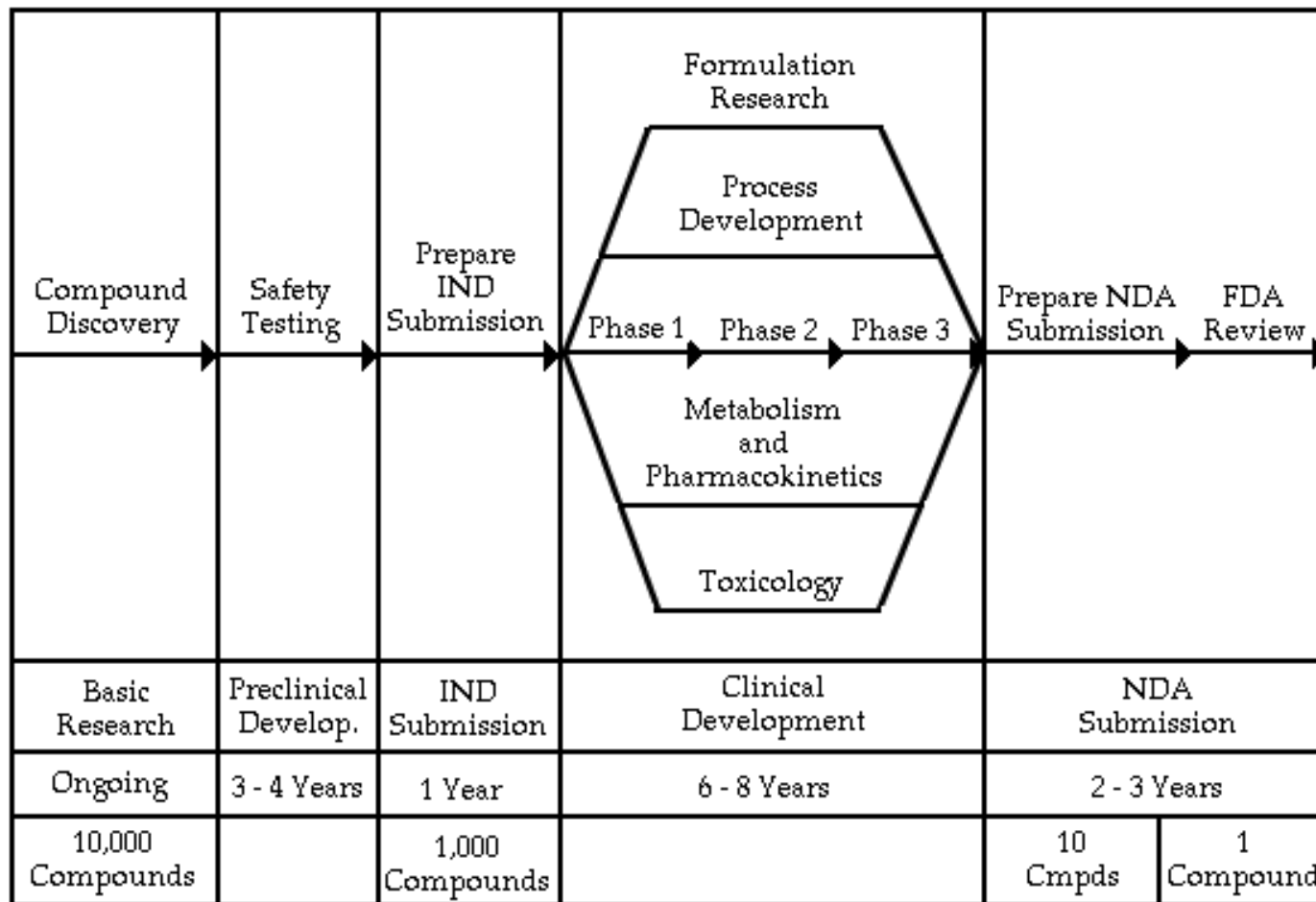
Vaccines against IV

- The best way to protect yourself is get vaccinated annually.
 - **The "flu shot"** — an inactivated vaccine (containing killed virus) that is given with a needle, usually in the arm.
 - **The nasal-spray flu vaccine** — a vaccine made with live, weakened flu viruses that do not cause the flu (sometimes called LAIV for "live attenuated influenza vaccine" or FluMist®).
- Trivalent Vaccine for 2010-2011 flu season:
 - A/California/7/2009 (H1N1);
 - A/Perth/16/2009 (H3N2);
 - and B/Brisbane/60/2008.
- Recommended strongly for high risk population
 - Pregnant women
 - Children younger than 5, but especially children younger than 2 years old
 - People 50 years of age and older
 - People of any age with certain chronic medical conditions
 - People who live in nursing homes and other long-term care facilities
 - People who live with or care for those at high risk for complications from flu, including Health care workers
- Mild side Effects for most, though potentially fatal allergic reactions for some people
 - <http://www.cdc.gov/vaccinesafety/Concerns/H1N1/index.html>
 - Our of 82 million vaccinated, 1 in 10,000 reported adverse effects, and 10% of those are severe.
- New cell based production methods may provide doses of vaccines on demand within weeks, instead of months when using chicken eggs



<http://www.flu.gov/individualfamily/vaccination/index.html>

Typical Drug Discovery Process



IND: investigational new drug
Phase I: pharmacokinetics (ADME) and safety

Phase II: controlled trials for safety and efficacy

Phase III: Expanded trials involving hundreds to thousands

ADME: adsorption, metabolism, distribution and excretion

NDA: new drug application

FDA: federal drug administration

Reform: fast track and priority review – less than 1 year for FDA approval

<http://www.netsci.org/Courseware/Drugs/Intro/>

Informatics for Biology and Chemistry: bioinformatics and cheminformatics

Drug-like

Lead-like

MW < 500

MW < 350

ClogP < 5

ClogP < 3.0

Hydrogen bond donors < 5

Chemically stable

Hydrogen bond acceptors < 10

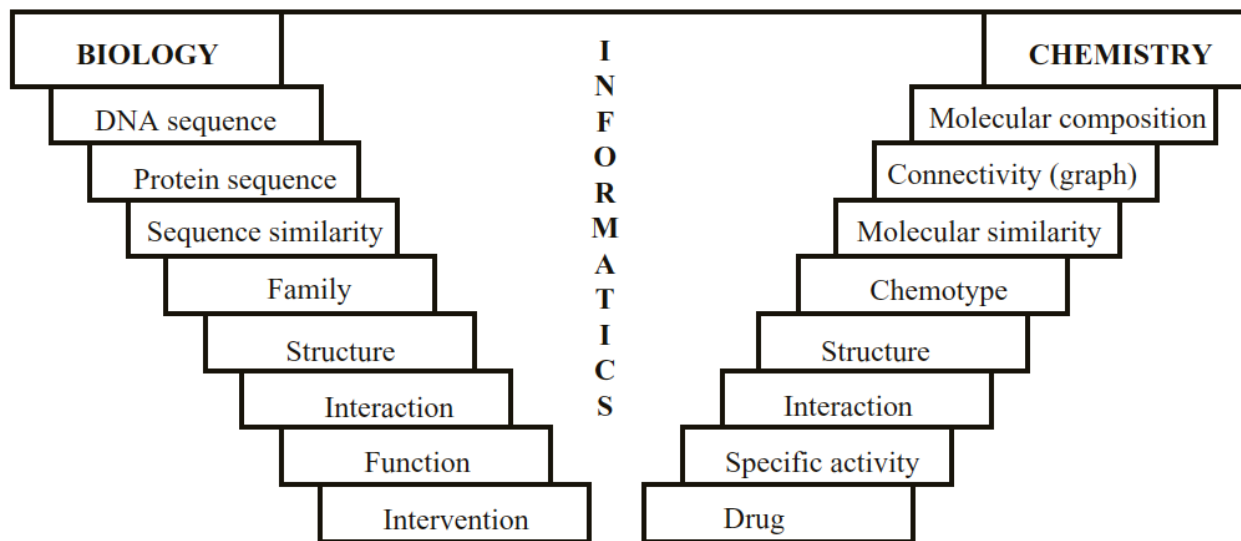
Number of rotatable bonds ≤ 10

PSA $\leq 140\text{\AA}^2$

Peptides not suitable

Non-substrate peptides suitable

Eliminate reactive functional groups, promiscuous inhibitors, and metabolically unstable compounds

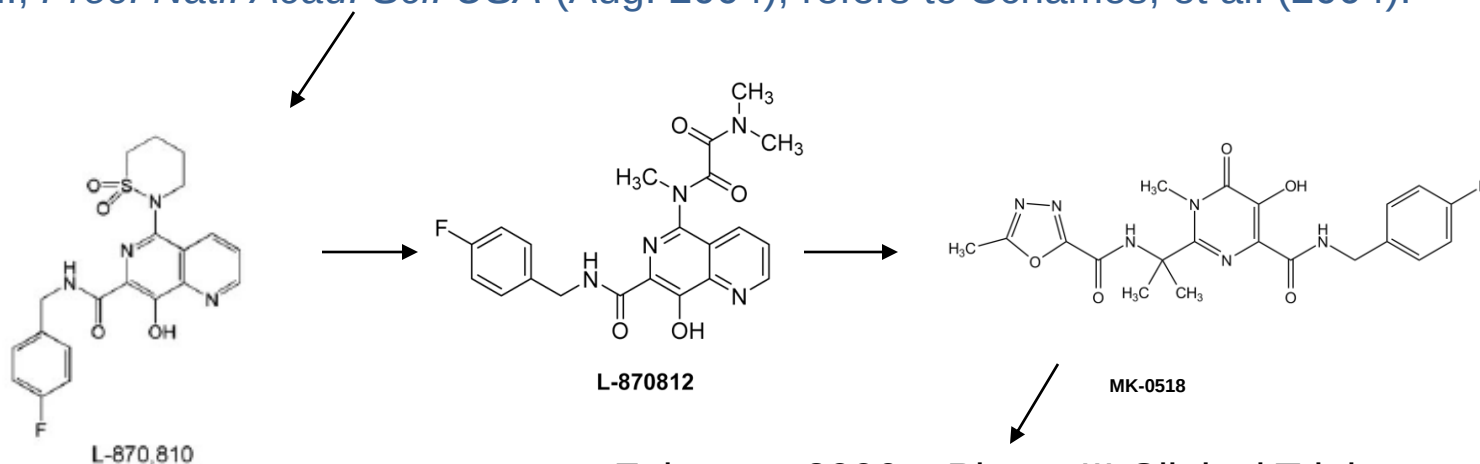


Bunin et al, Chemoinformatics, 2007

Relaxed Complex Scheme and Ensemble based Virtual Screening Contributed to HIV Integrase Inhibitor Development

Discovery of unexpected binding site in HIV-1 Integrase using MD and AutoDock:
Schames, ... & McCammon, *J. Med. Chem.* (released on web, early 2004)

“ Exploration of the structural basis for this unexpected result ... suggests an approach to the development of integrase inhibitors with unique resistance profiles.”
D. Hazuda et al., *Proc. Natl. Acad. Sci. USA* (Aug. 2004), refers to Schames, et al. (2004).



New Class of HIV Drugs: Merck & Co.

February, 2006 – Phase III Clinical Trials

February, 2007 – Name announced:

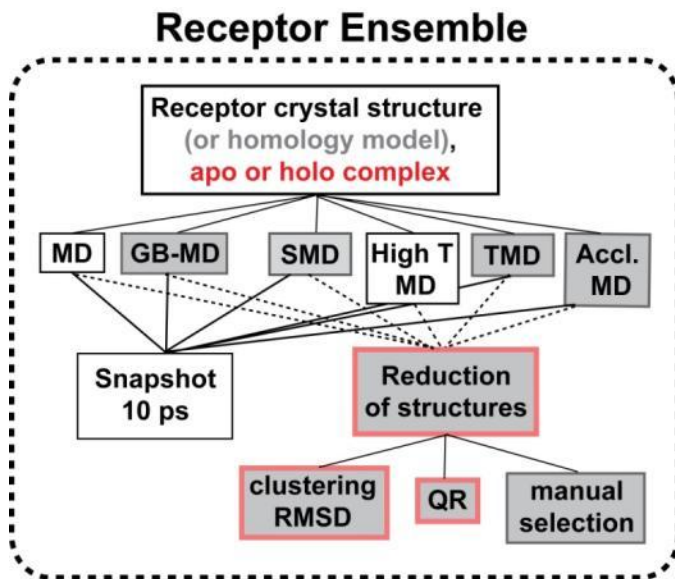
Isentress (raltegravir)

October, 2007 – FDA “fast track” approval

Source: A. McCammon

Ensemble-based Virtual Screening with Relaxed Complex Scheme

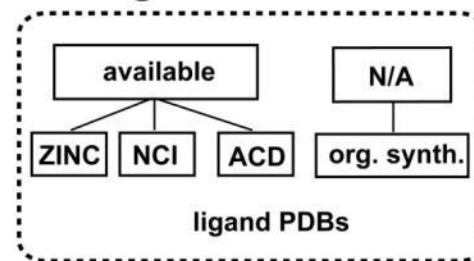
NAMD2
Amber



NCI Diversity Set: 3.3 MB, 2000 compounds;
Required at each site

ZINC subset: 200,000. A few hundred MB

Ligand Ensemble

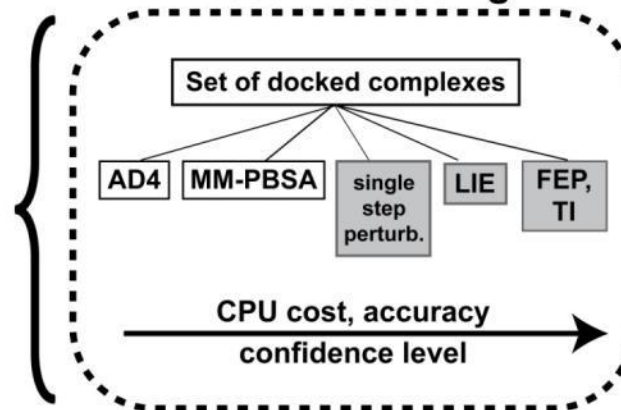


AutoDock4

AutoDock
(full ligand flexibility)

Docking Data: hundreds of MB

Post-Processing



Multiple targets: HA, NA subtypes
Each target: 30~50 MD snapshots, 1~2 MB each

Simulation Data: hundreds of GB

Experimental
verification

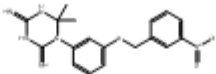
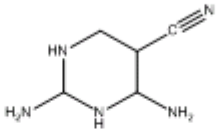
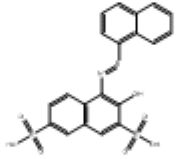
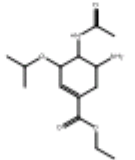
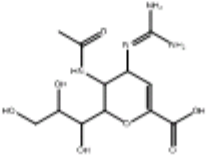
Known test set

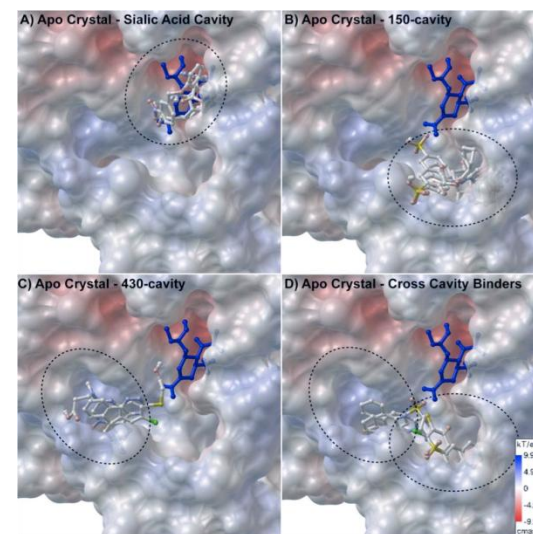
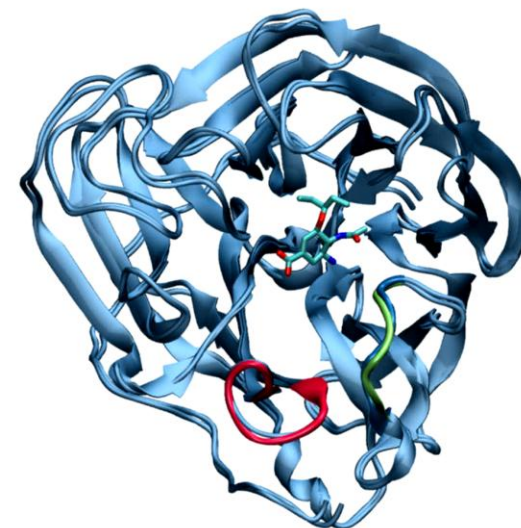
Total data to date: ~5 TB in long term storage.

Each experiment is about 1 Petaflops accumulative in computation cost.

Source: Amaro

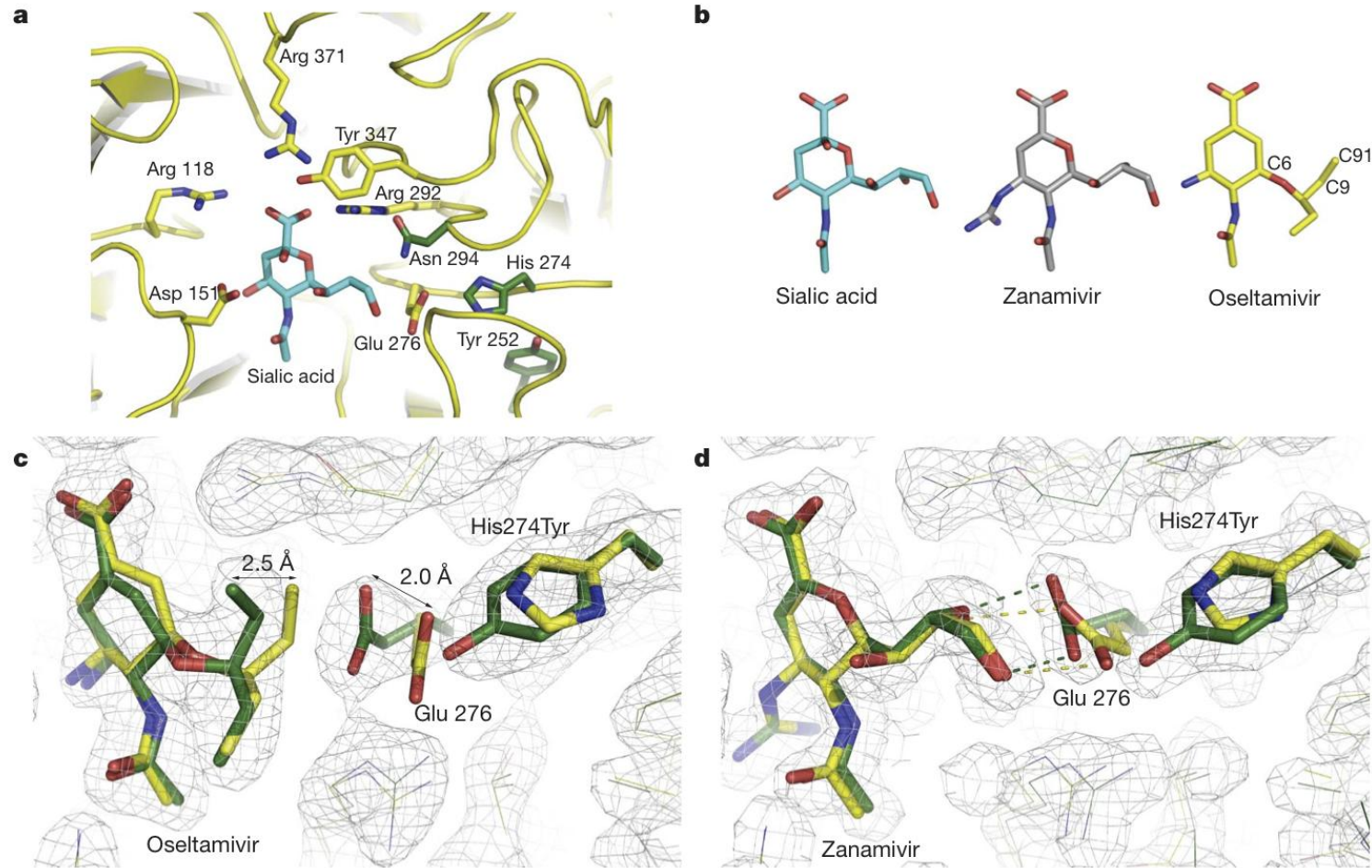
Ensemble based Virtual Screening of NCIDS1 Top Hits against NA

Rank	NSC	Mean Energy	Predicted K_i (μ M)	Chemical Structure	Binding Site	Apo Crystal Rank	Holo Crystal Rank
1	109836	-10.63	0.016		SA-cavity	15	1
2	211332	-10.34	0.026		SA-cavity	212	10
3	45583	-10.09	0.040		SA-cavity 150-cavity 430-cavity	6	18
-	Oseltamivir	-9.82	0.063 (0.3 – 1.0)		SA-cavity	238	5
-	Zanamivir	-9.38	0.133 (0.5 – 2.5)		SA-cavity	230	12



• Cheng et al, JMC, 2008

Mechanism of H275Y Resistance Mutation of N1

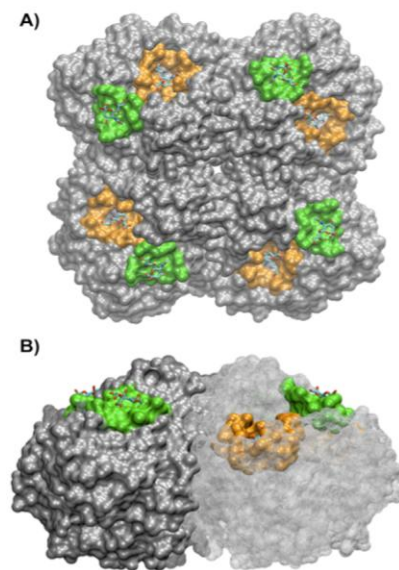


Collins PJ et al. Nature: 2008.

Electrostatic Steering and 2nd Sia binding site in Pandemic Influenza Virus

Table 1. Association Rates (k_{on}) of Ligands to the Active Site and Secondary Site of Neuraminidases from Three Influenza Strains^a

	$k_{on,active\ site}$ ($\mu M^{-1} \cdot s^{-1}$)	$k_{on,secondary\ site}$ ($\mu M^{-1} \cdot s^{-1}$)	$k_{on,secondary\ site}/k_{on,active\ site}$
Oseltamivir-N1-a	5.17 (8×10^{-4})	9.73 (1×10^{-3})	1.88
Sialic Acid-N1-a	9.41×10^{-2} (1×10^{-4})	208 (5×10^{-3})	2210
Oseltamivir-N2-h	12.1 (2×10^{-3})	84.2 (6×10^{-3})	6.96
Sialic Acid-N2-h	0.503 (5×10^{-4})	1.78 (1×10^{-3})	3.54
Sialic Acid-H1N1-h	0.168 (8×10^{-4})	12.6 (1×10^{-3})	75.0



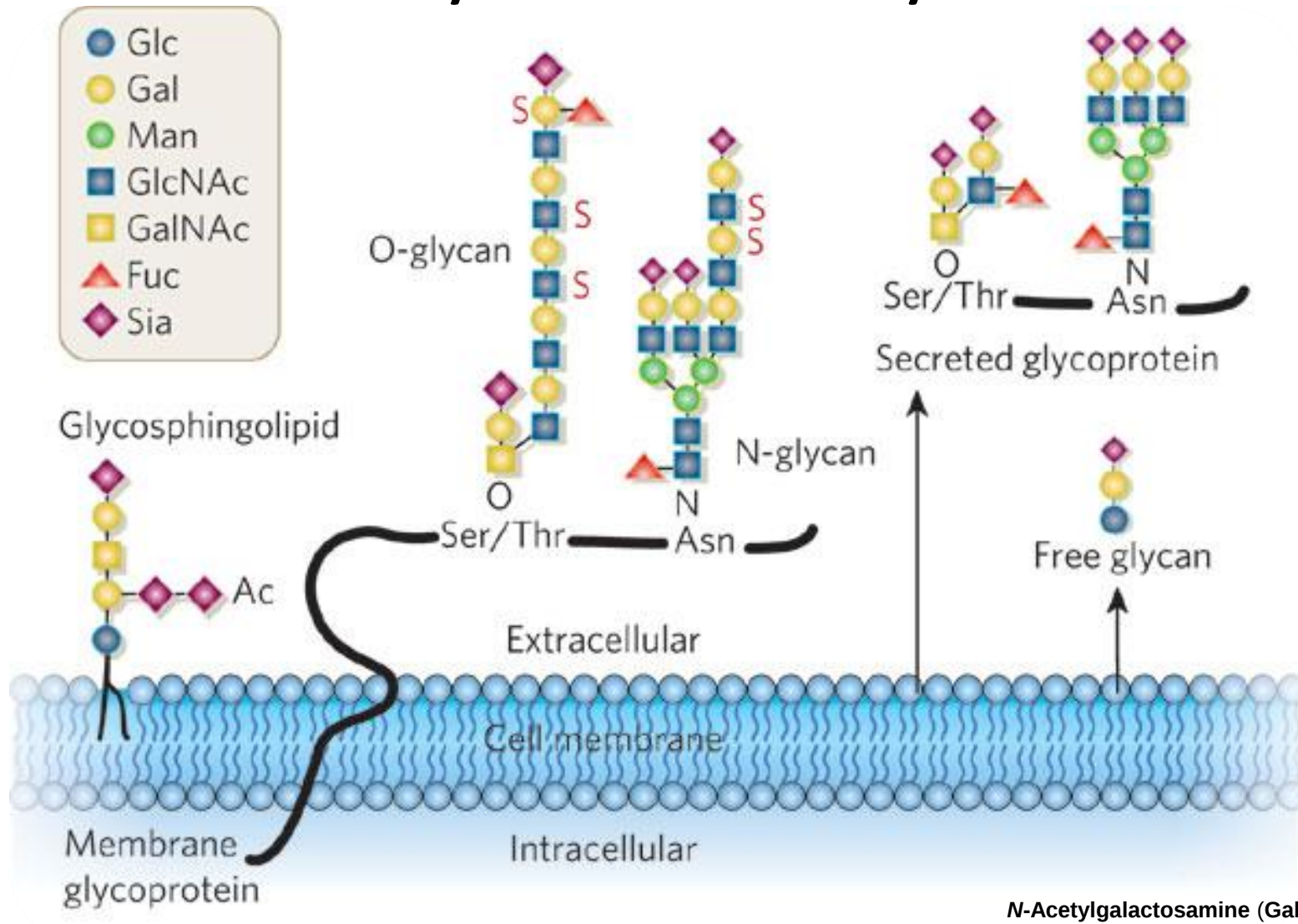
Green: 2nd site

a “-a” and “-h” denote avian- or human-derived strains, respectively. Standard errors of the mean are shown in parentheses.

	366-373	399-403	430-433
Avian N1	<u>K</u> S <u>T</u> N <u>S</u> R <u>S</u> G	A <u>I</u> T <u>D</u> <u>W</u> S	R <u>P</u> <u>K</u> E
Human N2	I <u>S</u> K <u>D</u> L <u>R</u> <u>S</u> G	D <u>S</u> D <u>N</u> R <u>S</u>	R <u>K</u> <u>Q</u> E
H1N1	<u>K</u> S <u>I</u> S <u>S</u> R <u>N</u> <u>G</u>	G <u>I</u> N <u>E</u> <u>W</u> S	R <u>P</u> <u>K</u> E

Sung et al, JACS, 2010

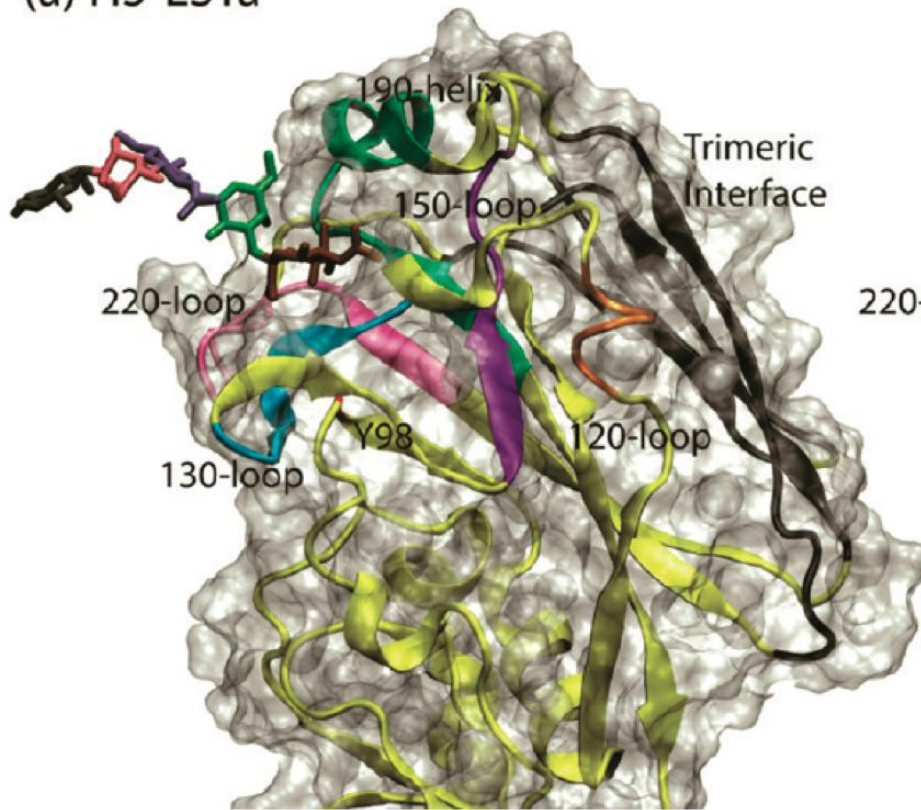
Glycan Diversity



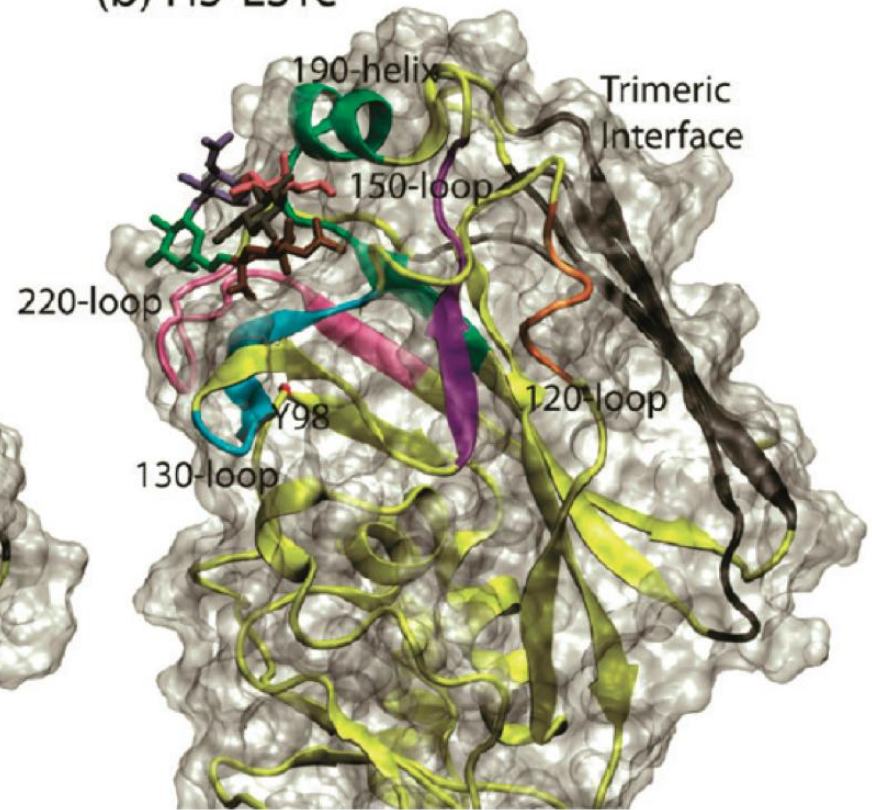
N-Acetylgalactosamine (GalNAc)

HA-Glycan Receptor Binding Domain

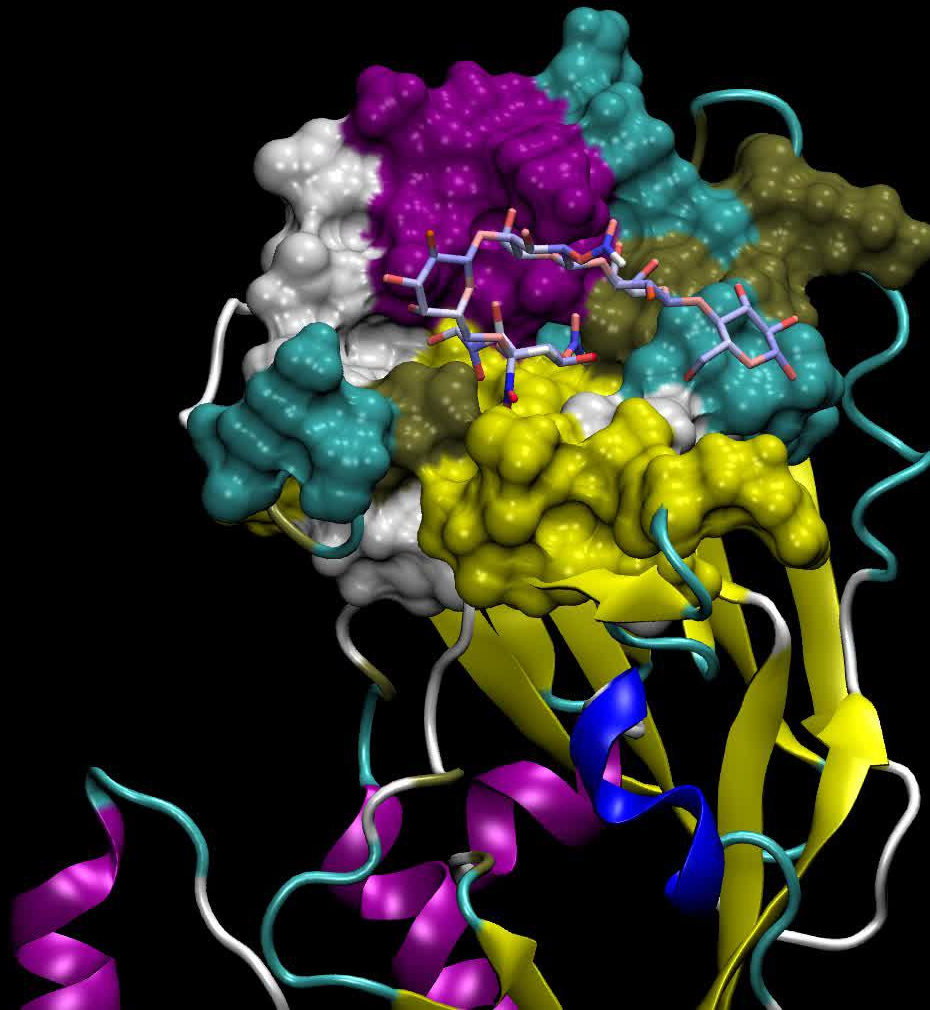
(a) H5-LSTa



(b) H5-LSTc

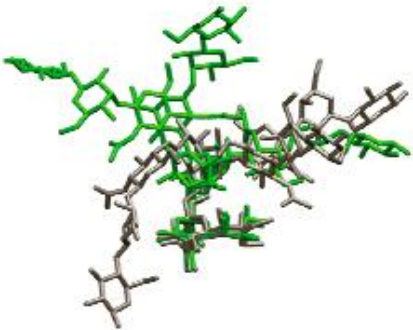


Visualization of HA-Glycan Interactions

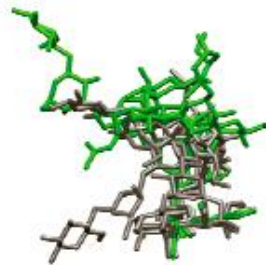


Glycan topology and induced conformational changes

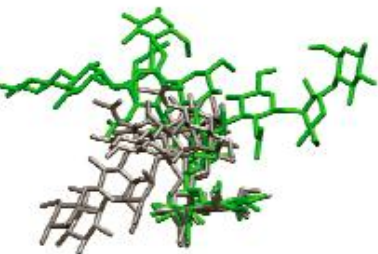
Unbound LSTa/LSTc



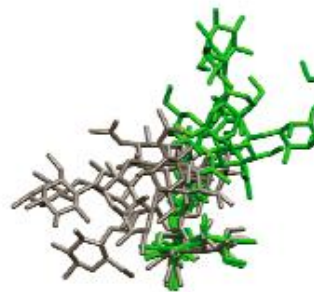
(b) LSTa-H3/LSTc-H3



LSTa-H5/LSTc-H5



(d) LSTa-H9/LSTc-H9



Free: green; Bound: Gray

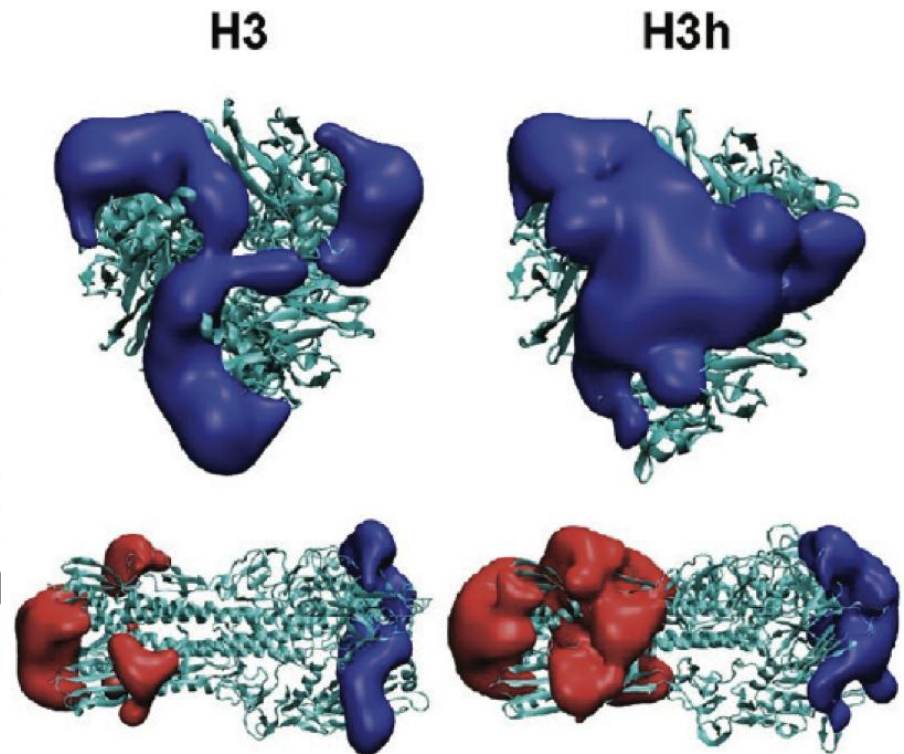
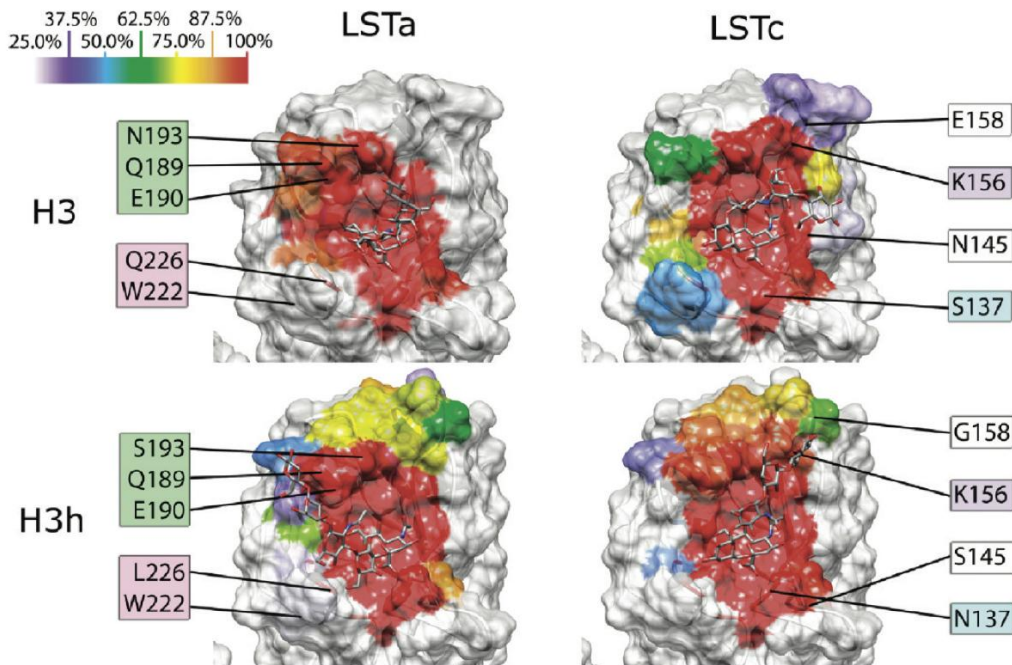
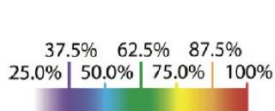
Table 4. Glycan conformational entropic changes between bound and free states.

		H3	H5	H9
LSTa	$-\Delta S_{\text{Conf}}$	1.59 (0.34)	0.28 (0.01)	2.46 (0.02)
	$-\Delta S_{\alpha-2,3}$	0.79 (0.18)	0.13 (0.03)	1.89 (0.03)
	% Contribution	50%	46%	77%
LSTc	$-\Delta S_{\text{Conf}}$	2.47 (0.80)	5.52 (0.11)	4.85 (1.64)
	$-\Delta S_{\alpha-2,6}$	1.39 (0.45)	3.55 (0.06)	2.49 (0.82)
	% Contribution	56%	64%	38%
	$\Delta(-\Delta S_{\text{Conf}})$	0.88 (0.43)	5.24 (0.06)	2.39 (0.82)

The percent contribution is $-\Delta S_{\alpha-2,3}$ or $-\Delta S_{\alpha-2,6}$ relative to $-\Delta S_{\text{Conf}}$. Standard errors are given in parenthesis. All units are in kcal/mol. Temperature is 310K. $\Delta(-\Delta S_{\text{Conf}})$ is the difference between $-\Delta S_{\text{Conf}}$ of LSTc and LSTa bound to the same HA. Standard errors are given in parenthesis.

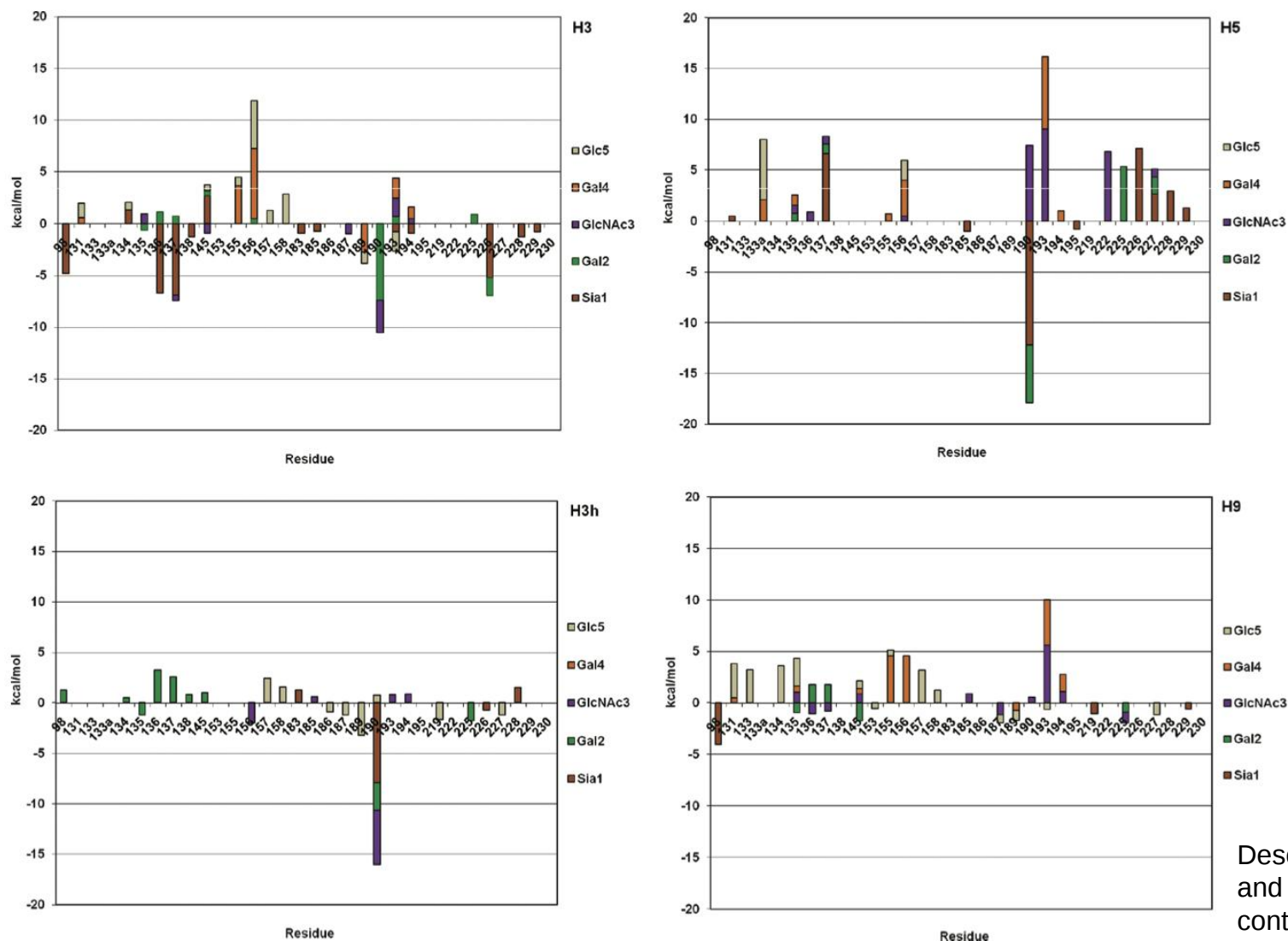
Xu et al, JMB, 2009

Role of Electrostatic Steering in Receptor Specificity Switch



Newhouse et al, JACS, 2009

Propensity Index from Interaction Energy Analysis for HA Receptor Domain Residues

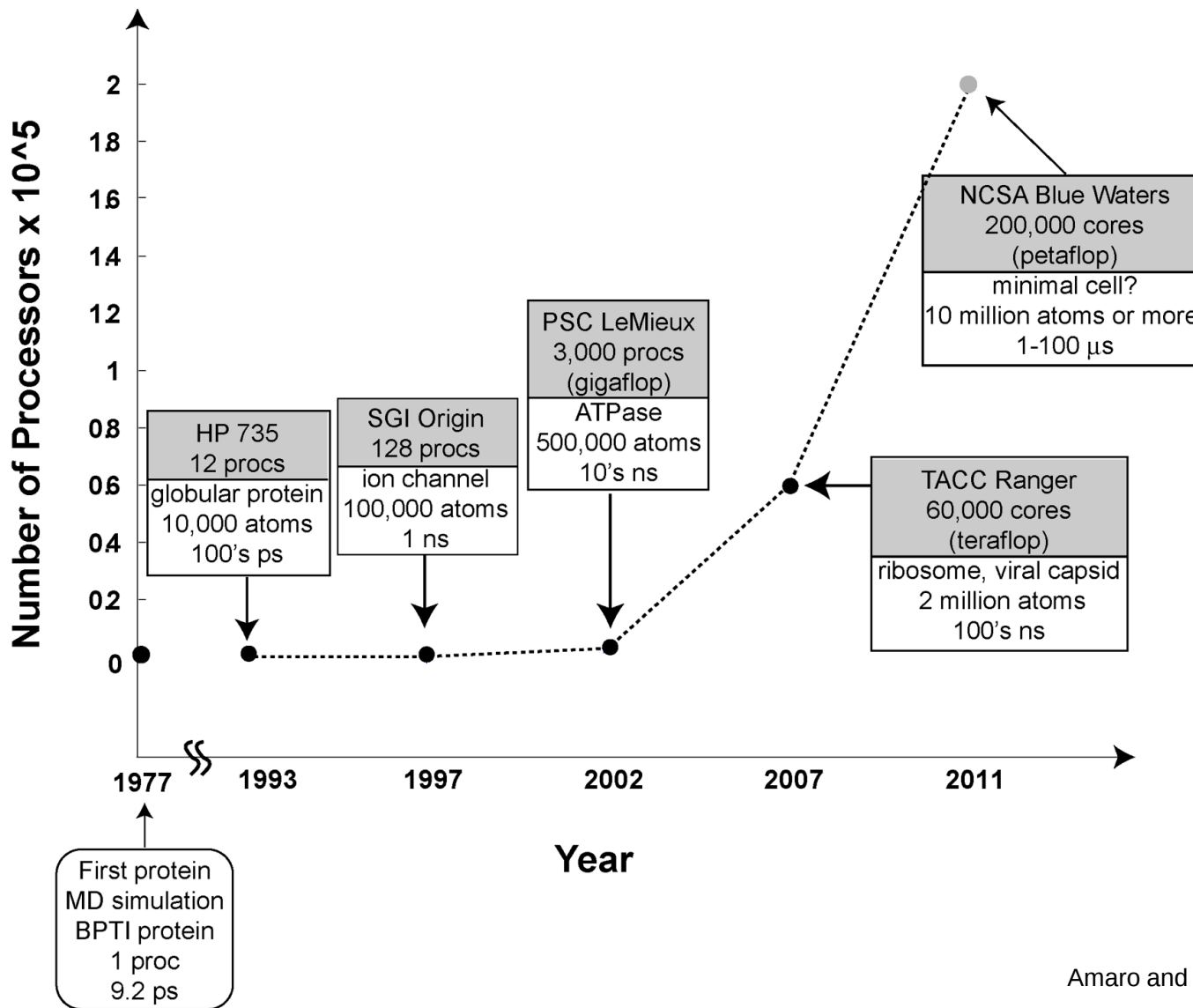


Desolvation Energy and Entropic contributions ignored

Figure 7. Propensity index for RBD residues to favor LSTa or LSTc in bound state. Negative values favor bound LSTa, and vice versa for bound LSTc.

Newhouse et al, JACS, 2009

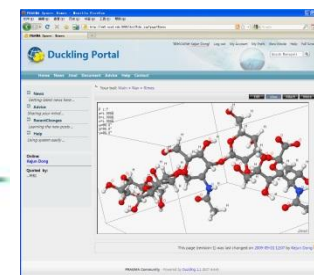
Computing Power Readily Available at Supercomputer Centers



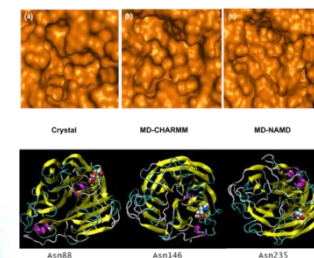
Amaro and Li, CTMC, 2010

Transparent access of applications on Avian Flu Grid through middleware

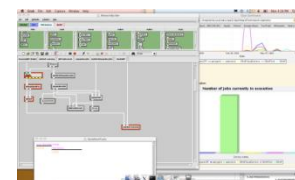
Avian Flu Grid



CNIC Duckling Portal



Konkuk Glyco-M*Grid



NBCR CADD

IaaS – Infrastructure as a Service – Cloud with the most promise

The left column of screenshots shows three early cloud computing services:

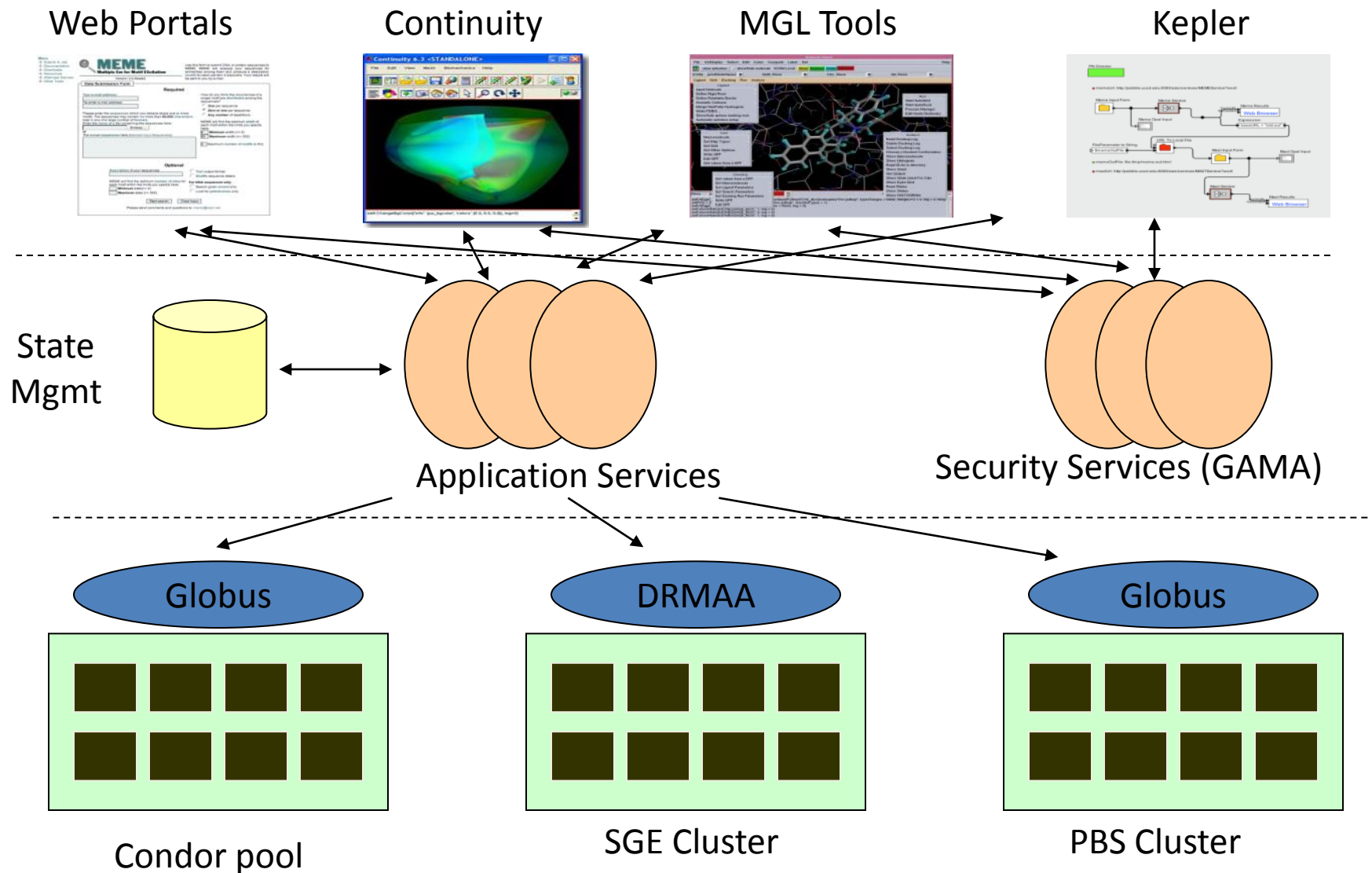
- Sun:** A screenshot of the Sun Microsystems website from 2005, titled "TAP INTO THE POWER OF NETWORK.COM". It promotes flexible access to pay-per-use computing resources.
- 3Tera:** A screenshot of the 3Tera website, titled "Cloud Computing For Web Applications". It features a sunflower image and lists services like "Outsourced Services" and "Integrated Web Services".
- IBM:** A screenshot of the IBM Cloud Computing website, titled "IBM Building its Eighth and Ninth Clouds". It includes a "Cloud Computing News Desk" and mentions the "ANALYSTS' VIEW Conference".

The right column of screenshots shows two more prominent cloud services:

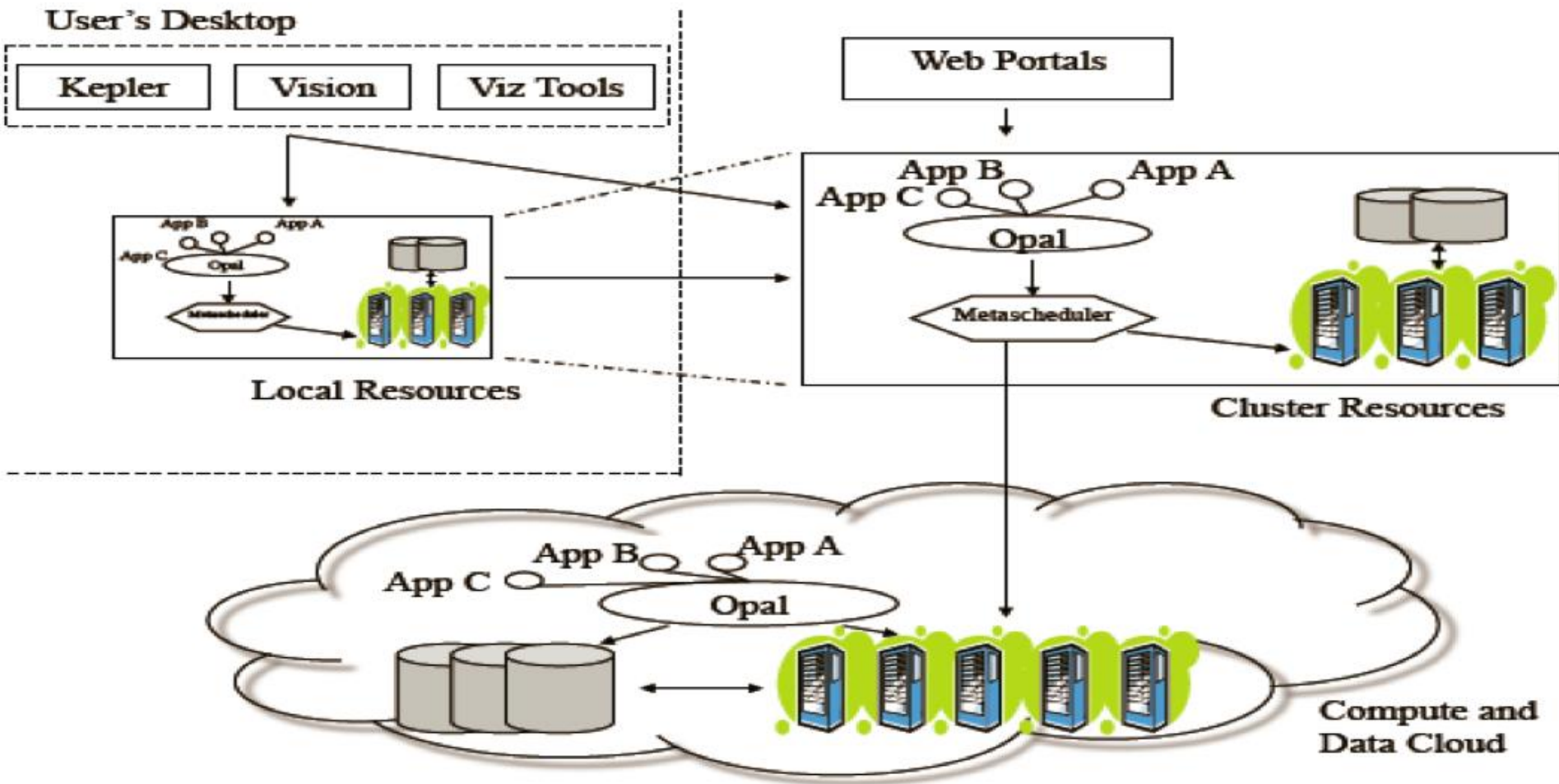
- Amazon EC2:** A screenshot of the Amazon Elastic Compute Cloud (Amazon EC2) page, titled "Amazon EC2". It describes it as a web service that provides resizable compute capacity in the cloud.
- GoGrid:** A screenshot of the GoGrid website, titled "Finally, a hosting service that delivers real CONTROL IN THE CLOUD™". It features a "Sign up for the Public Beta" button and lists supported operating systems like Windows Server 2003 and 2008.

Run (virtual) computers to solve your problem, using your software

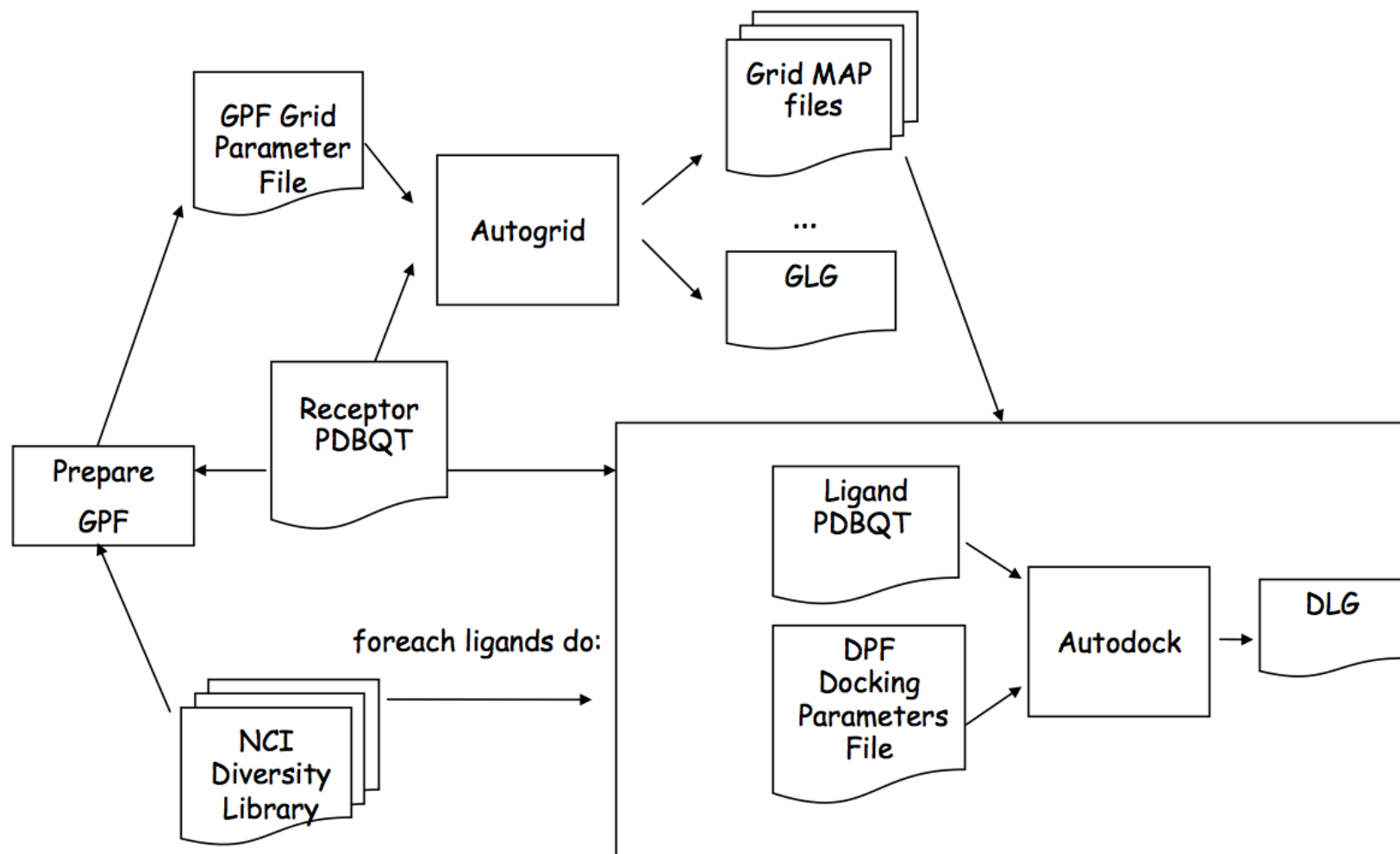
NBCR Opal Web Service Toolkit v1



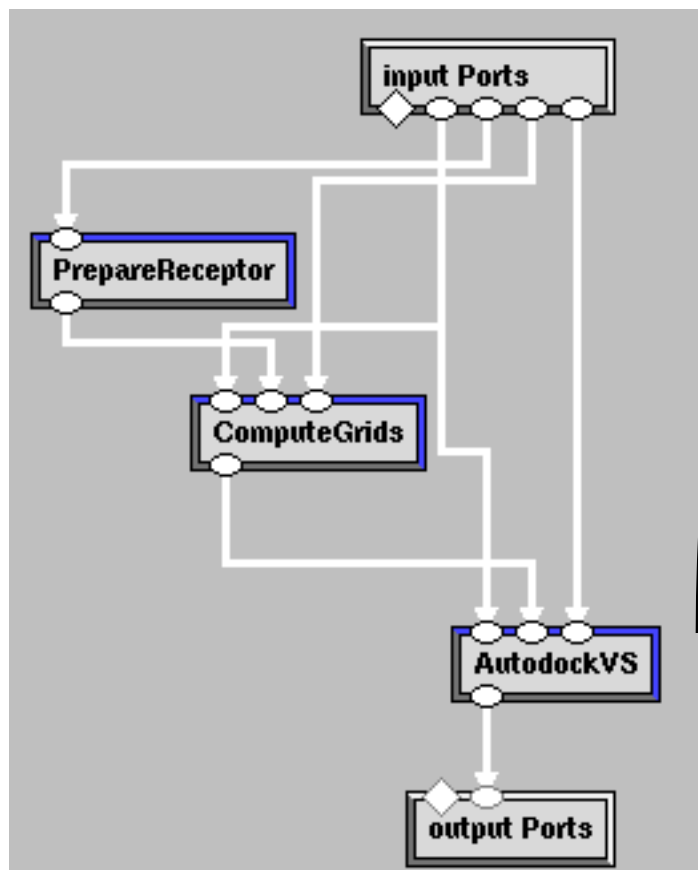
Opal 2 for SaaS



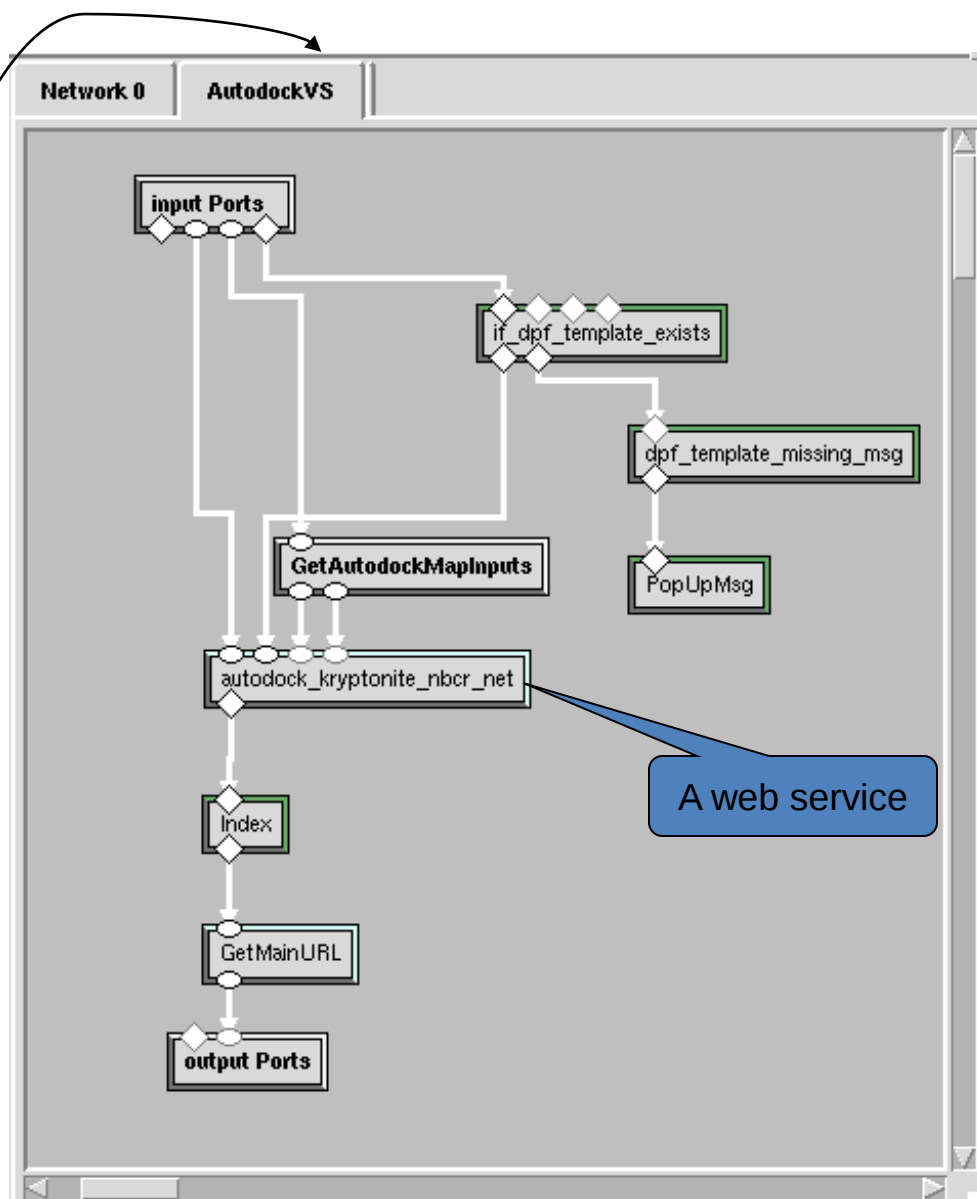
AutoDock Workflow



A Virtual Screening Vision Workflow



Ren et al, NAR, 2010



Vision Based Grid Workflow Environment

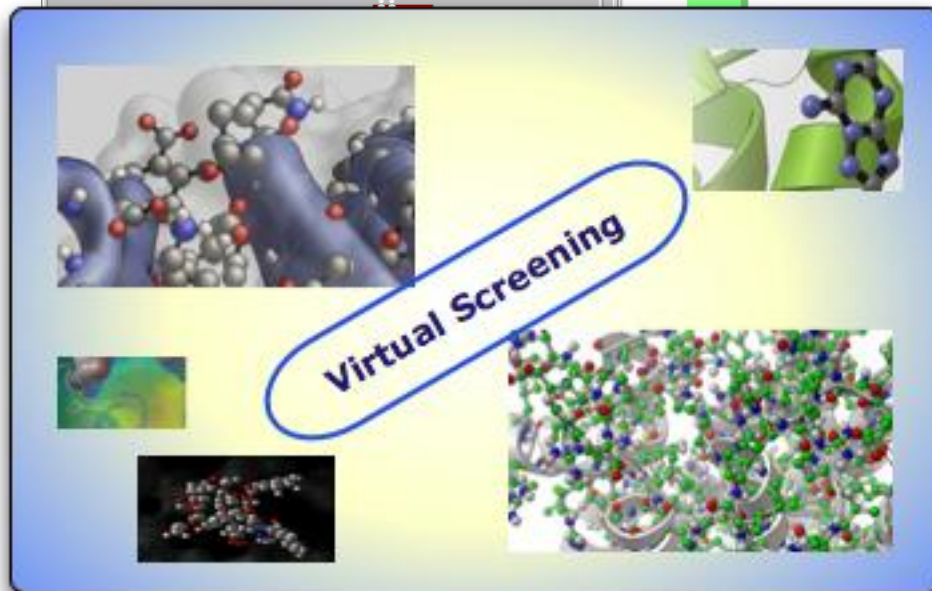
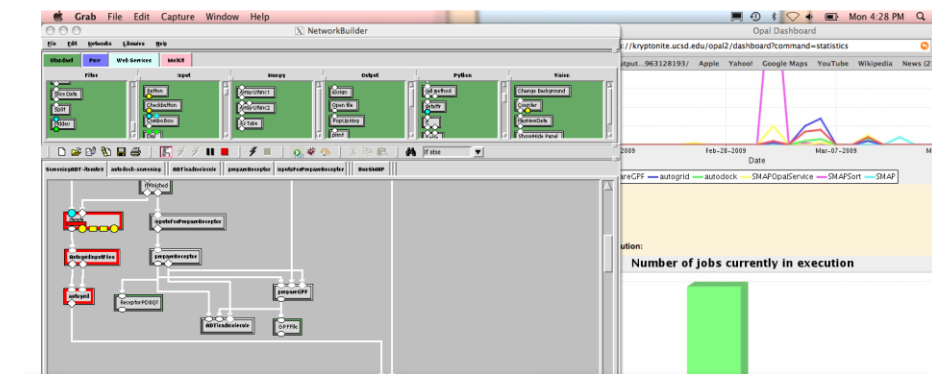
The image displays two software windows from the Vision Based Grid Workflow Environment.

Python Molecule Viewer: This window shows a 3D molecular model of a protein-ligand complex. The protein surface is colored by electrostatic potential, with a color scale on the left ranging from -10 (red) to 10 (blue) in units of kT/e . The ligand is shown as a stick model. The interface includes a menu bar (File, Edit, Select, 3D Graphics, Display, Color, Compute, Grid3D, Help), a toolbar with various 3D manipulation tools, and a bottom panel with selection and display options.

NetworkBuilder: This window shows a workflow graph for a molecular simulation. The workflow starts with a 'Pdb2pqrOpalServiceOpalWrap' node, followed by a 'Split' node. The workflow then branches into three parallel paths, each starting with a 'Pmv' node. These paths converge at a 'Run APBS Map Potential2MSMS' node. The workflow then proceeds to a 'Run APBS' node, followed by a 'Choose Molecule' node (set to '1hpx'), a 'Get MSMS Geom' node, a 'Map Pot On Geom' node, and finally a 'Pmv Viewer' node. The interface includes a menu bar (File, Edit, Networks, Libraries, Help) and a toolbar with various workflow management tools.

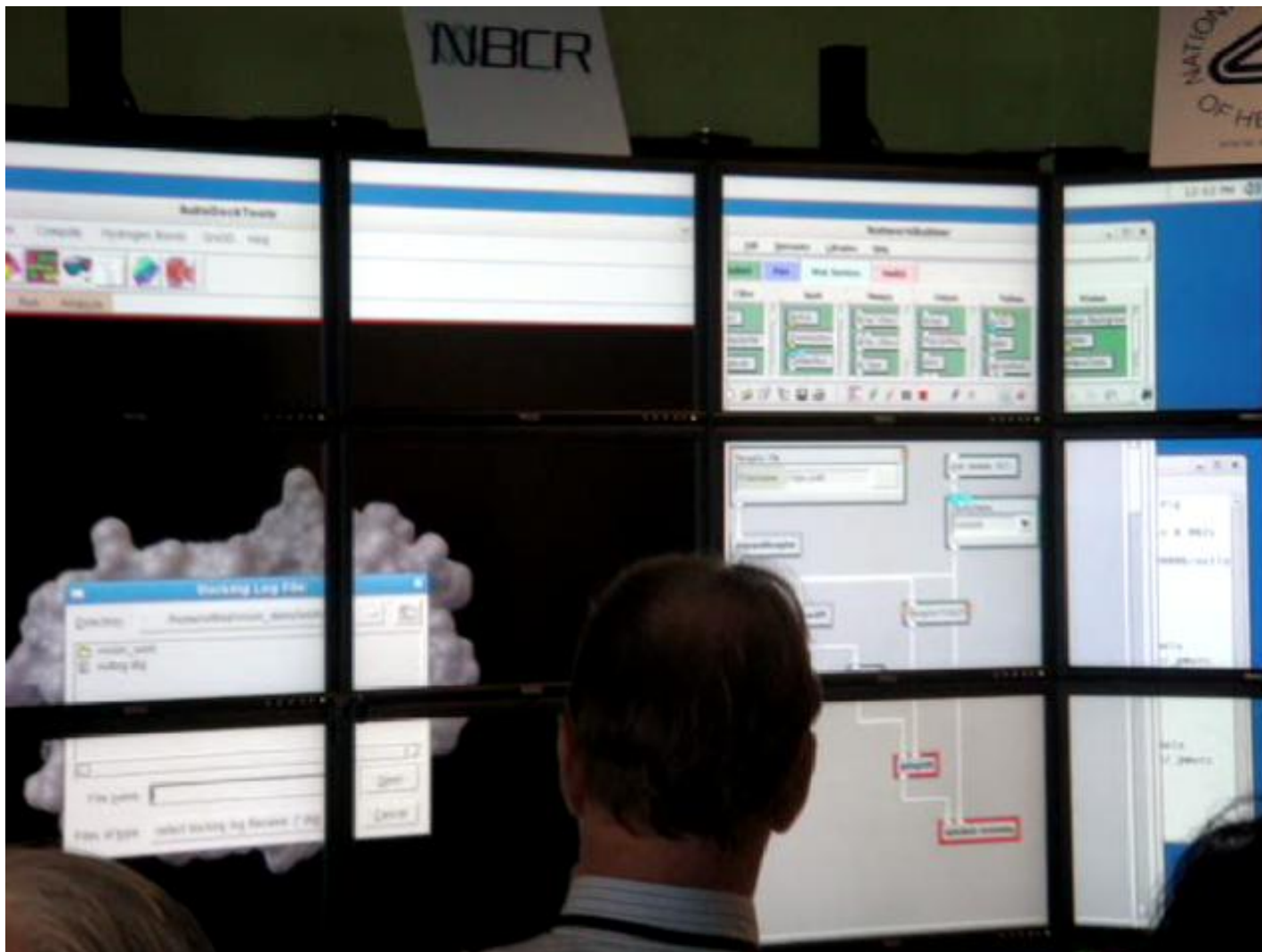
Clementi et al, IEEE eScience 2008

Service as Software: CADD Workflows based upon distributed services



<http://cadd.nbcr.net>

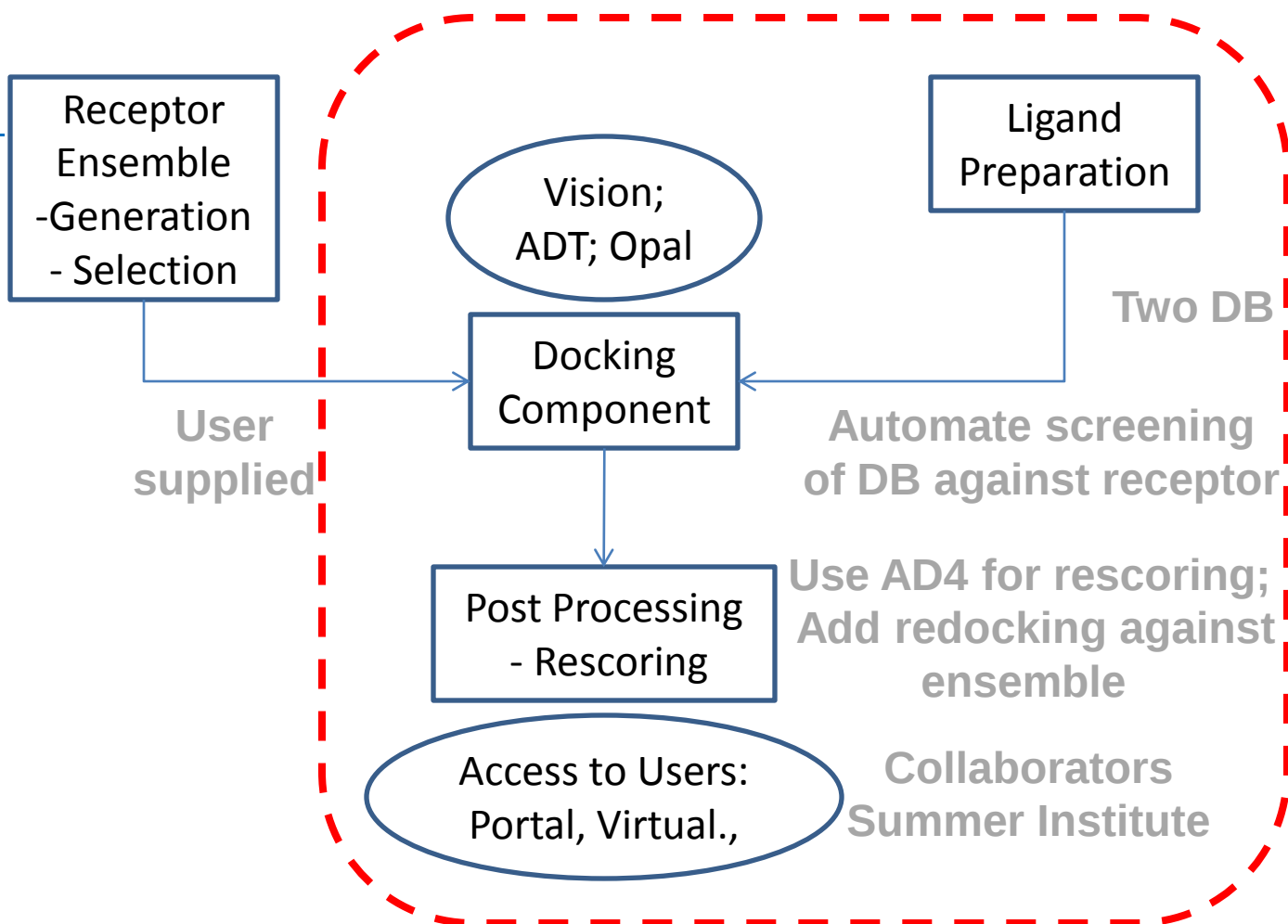
CADD Pipeline



Phase 3: CADD Pipeline

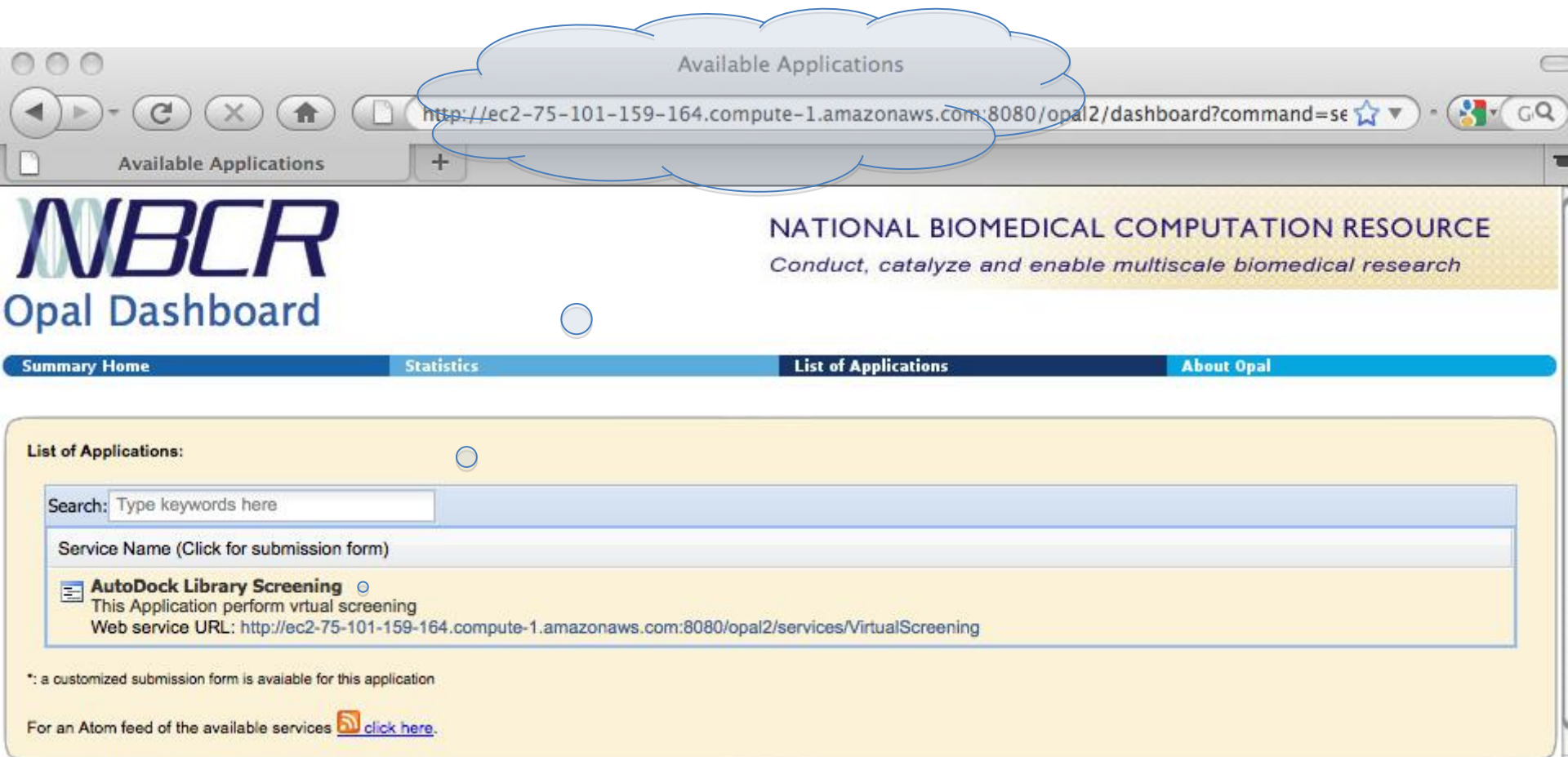
End of Year 2 (April 2011)

RMSE-based
clustering;
QR factor-
ization



Source: Amaro

Cloud Computing with Amazon EC2



The screenshot shows a web browser window with the URL `http://ec2-75-101-159-164.compute-1.amazonaws.com:8080/opal2/dashboard?command=se`. The browser's address bar and the page's title bar both display "Available Applications". The page content includes the NBCR logo, the text "Opal Dashboard", and the heading "NATIONAL BIOMEDICAL COMPUTATION RESOURCE" with the tagline "Conduct, catalyze and enable multiscale biomedical research". A navigation bar contains links for "Summary Home", "Statistics", "List of Applications", and "About Opal". The "List of Applications" section features a search bar and a list of services. The first service listed is "AutoDock Library Screening", which includes a description and a web service URL: `http://ec2-75-101-159-164.compute-1.amazonaws.com:8080/opal2/services/VirtualScreening`. A note at the bottom states: "a customized submission form is available for this application". A link for an Atom feed is also provided.

Kepler Opal Web Services Actor

The screenshot displays the Kepler IDE interface with the 'Pdb2pqr' actor selected in the workflow canvas. The 'Edit parameters for Pdb2pqr' dialog box is open, showing the following configuration:

Parameter	Value
serviceURL:	http://ws.nbcrc.net/opal/services/Pdb2pqrOpalService
numberOfExtraInputFiles:	0
class:	edu.sdsc.nbcrc.opal.OpalClient
semanticType00:	urn:lsid:localhost:onto:1:1#WebServiceActor
semanticType11:	urn:lsid:localhost:onto:2:1#WebService
inFile:	Browse
inId:	
forcefield:	AMBER
output-file:	output.pqr
ffout:	
chi:	☐
phi:	☐
psi:	☐
rama:	☐
hbond:	☐
with-ph:	
ligand:	
verbose:	☒
nodebump:	☐
noopt:	☐
chain:	☐
assign-only:	☐
clean:	☐
apbs-input:	☐

Buttons at the bottom of the dialog: Commit, Add, Remove, Restore Defaults, Preferences, Help, Cancel.

Vistrails and Opal Service for APBS

Terminal — vistrails — 130x19

```
http://ws.nbcrc.net/opal2/services/OpalService is going to execute the command: lhp.in.pot
Job outputs URL: http://ws.nbcrc.net/app1272581292545
Opal job completed successfully
('http://ws.nbcrc.net/app1272581292545/stdout.txt', 'http://ws.nbcrc.net/app1272581292545/stderr.txt', 'http://ws.nbcrc.net/app1272581292545/lhp.pqr', 'http://ws.nbcrc.net/app1272581292545/lhp.in.pot', 'http://ws.nbcrc.net/app1272581292545/io.mc', 'http://ws.nbcrc.net/app1272581292545/lhp.potential.dx')
```

VisTrails Builder – apbs_ws.vt*

Modules

Basic Modules

- Boolean
- Color
- ConcatenateString
- Constant
- Directory
- File
- FileSink
- Float
- Group
- InputPort
- Integer
- List
- Module
- Null
- OutputPort
- Path
- PythonSource
- SmartSource
- StandardOutput
- String
- SubWorkflow
- TestTuple
- Tuple

apbs_ws.vt*

File

List

Execute OpalJob

StandardOutput

Methods

Method	Signature
ExecuteOpalJob	
commandline	(String)
numProcs	(Integer)
url	(String)
Module	

Set Methods

commandline

String lhp.in.pot

url

String al2/services/OpalService

Nimrod/K and Opal Service for AutoDock4

The screenshot displays the Nimrod/K Director interface. The main window shows a workflow diagram at the bottom with steps: 'Nimrod/K Director', 'Opal', 'Opal Display', 'Opal Display2', 'Display', and 'Display2'. The 'Opal Display' and 'Opal Display2' windows are open, showing a list of URLs from the kryptonite.nbcr.net server. The 'Opal Display' window shows URLs for output.glg, summarize_results.txt, seeds_file, diversity0003, 2HU4_B.maps.xyz, diversity0002, 2HU4_B.HD.map, wget.out, diversity0004, and 2HU4_B.NA.map. The 'Opal Display2' window shows URLs for 10700, 10701, 10985, 10989, 10697, 10994, 11623, 10979, 11620, and 11617. The status bar at the bottom indicates 'execution finished.'

Enticott et al, PRAGMA 18

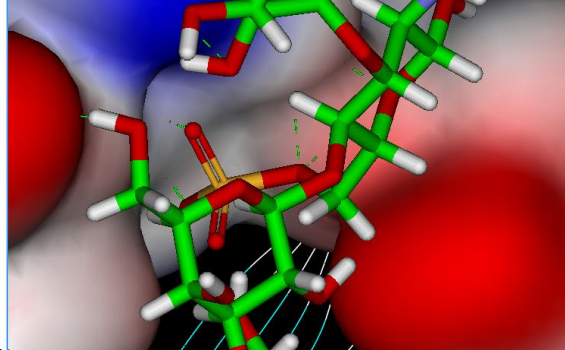
Social Networks and Collaborative Environment

Social Network Site	Number of Users	Features	API Examples
Google	170 million (Gmail)	Google Integrated Suite of Tools	Google Apps Engine
LinkedIn	65 million	Professional	Huddle/Zoho Office Online
Twitter	100 million	Short MMS/SMS	TwitPic
Google Wave	100,000 X 7?	Upload any file	Google Wave Robot
Facebook	500 million+	Social network	Facebook Apps

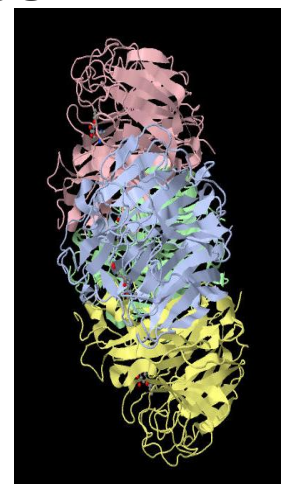
Are these too big to fail?
Utility Computing finally?

PRIME 2010

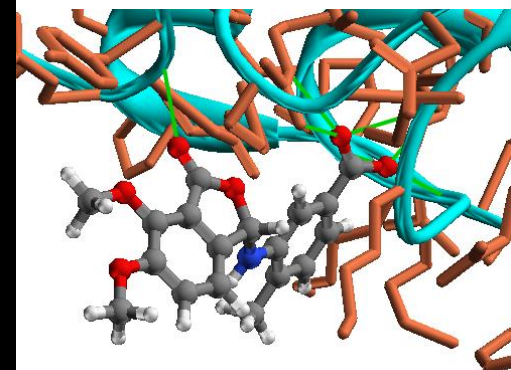
- 13 host sites
- Expanded to five sites S. Chang, USM



- Doshisha University, Kyoto
- National Institute of Information and Communication Technology (NiCT)
- National Museum of Marine Biology and Aquarium (NMMBA), Kenting, Taiwan,
- National Taiwan University (NTU),
- University of Hyderabad



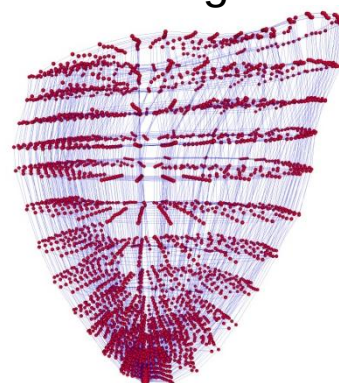
Jade Kwan, NiCT



C. Wong CNIC

M. Mui, U Hyderabad

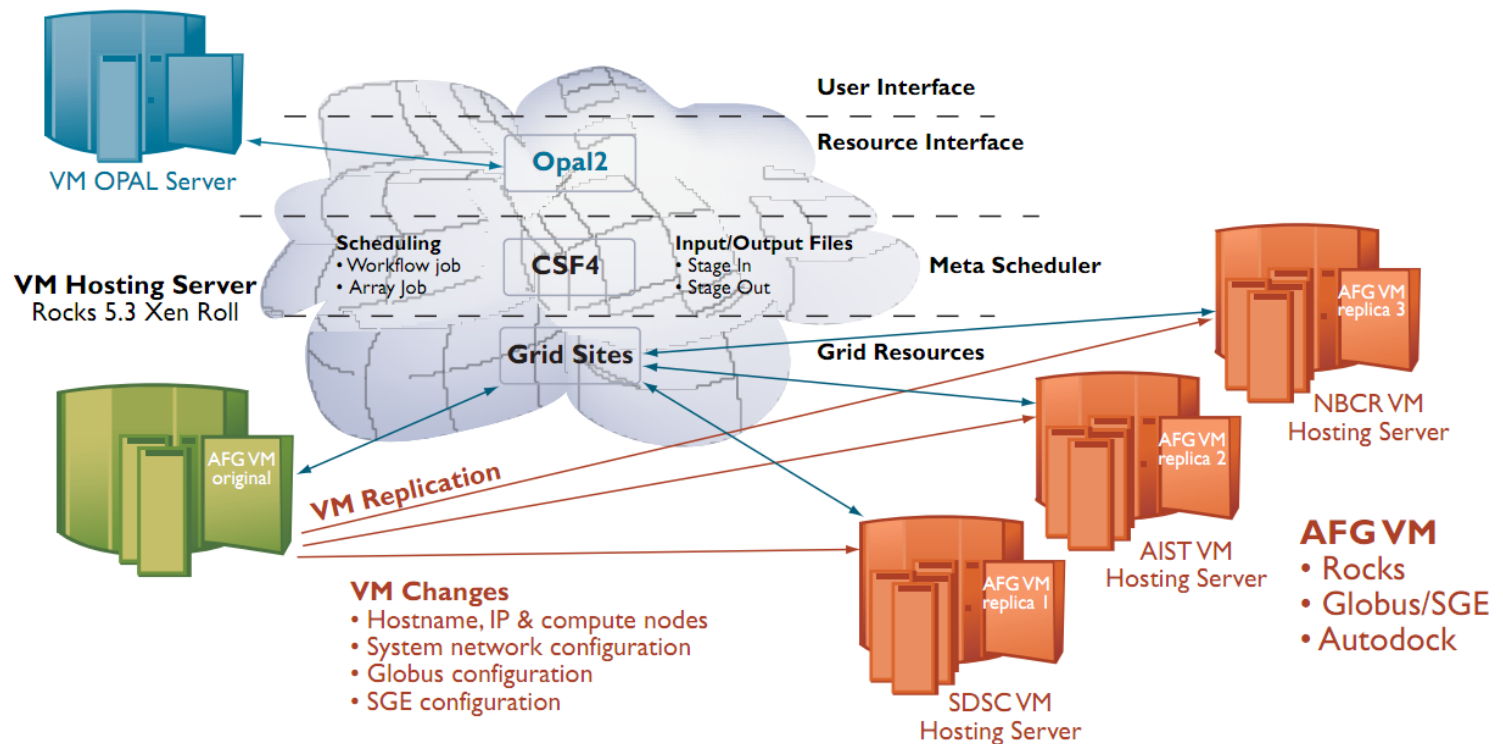
- Continued at eight sites
 - Monash U; NCHC; Osaka U; CNIC; NCREE; USM; U Auckland; U Waikato



C Lau, Osaka

PRAGMA: model for international collaboration in Technology and Science

Fig. 1 PRAGMA Rocks Virtualization Experiment



Broadening Impact of Technology Engaging Future Generations



PRIME Student 2009: Jessica Hsieh, USM



PRAGMA 18

Like the Grid

Like the Cloud



La Jolla, California – UC San Diego
March 2-5, 2010

March 2 – PRAGMA Institute on Implementation
& Welcome Reception

March 3-4 – PRAGMA Workshop

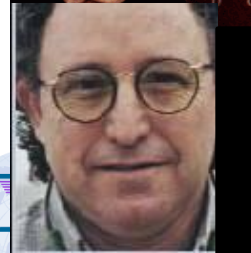
March 5 – Technology for Coral Reef Observatory



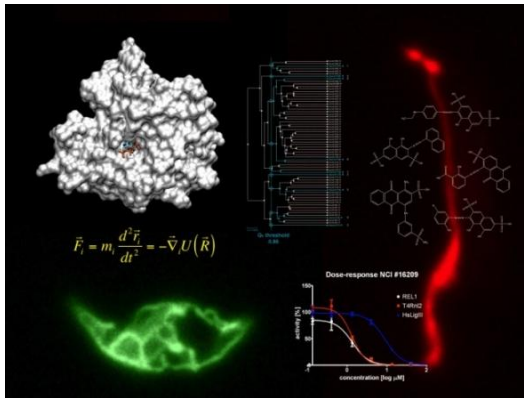
NBCR Researchers

Leading Interdisciplinary Team

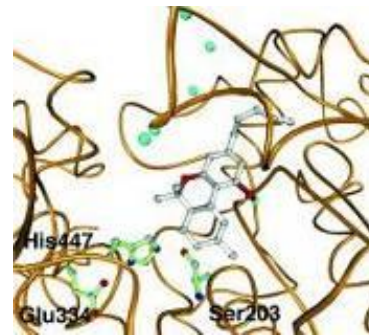
- J. Andrew McCammon, Chemistry
- Rommie Amaro, Chemistry
- Michael Holst, Math
- Nathan Baker, Chemistry/Math
- Zeyun Yu, Comp Science
- Anushka Michailova, Biophysics
- Peter Arzberger, Math/Pop BIO
- Andrew McCulloch, Bioengineering
- Roy Kerckhoff, Bioengineering
- Michel Sanner, Comp Science
- Art Olson, Chemistry
- Mark Ellisman, Neuro,
- Philip Papadopoulos, Electrical Engineering
- Wilfred Li, Biochemistry



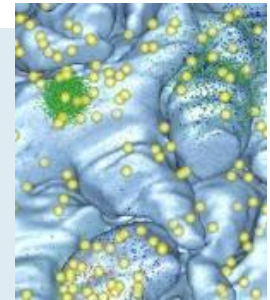
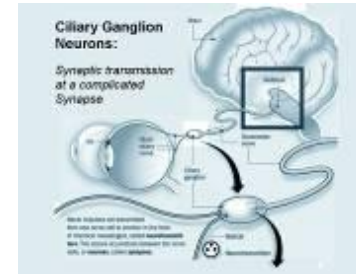
Biomedical Advances Powered by NBCR Tools



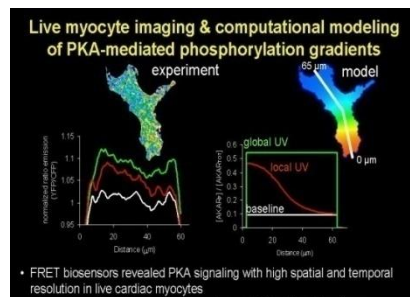
African Sleeping Sickness,
Amaro et al,
PNAS 2008



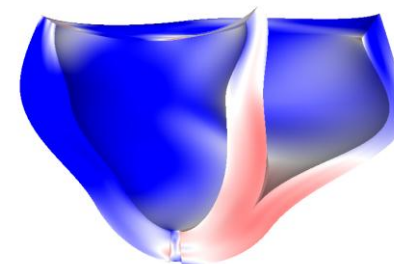
Alzheimer's Treatment
Eubanks et al, Mol.
Pharm 2006



Neurotransmission
Insight: Imaging and
Modeling; Coggan et al
Science 2005



Imaging, Modeling and
Cell-level Understanding
Saucerman et al
PNAS 2006



Biventricular pacing
and scar size
Kerckhoffs et al.. Med
Image Analysis 2008

2008

SUMMER INSTITUTE

LA JOLLA, CALIFORNIA 4-13 AUGUST 2008

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- Cluster/Grid Computing & Workflow Management
- Programming Scalable Scientific Applications
- Virtual Screening & Computer Aided Drug Design
- Computational Cardiac Electrophysiology and Mechanics
- Molecular Electrostatics and Diffusion
- Multiscale Imaging Analysis and Visualization

Builds Community



Leads to improved on-line training materials

<http://si.nbcr.net>



Acknowledgment

Science:

- *Irene Newhouse*
- *Dong Xu**
- **Youngjin Choi**
- Hsing Pao
- **Jung-Hsin Lin**
- **Habibah Wahab**
- Maqsudul Alam
- *Doman Kim*

Technology:

- Zhaohui Ding
- Guanyuan Liu
- **Osamu Tatebe**
- Yusuke Tanimura
- Jonghyun Lee
- **Kai Nan**
- **Xiaohui Wei**
- **Suntae Hwang**
- Aimee Li, MURPA

Collaborators:

Peter Arzberger, UCSD
David Abramson,
Monash University,
MUPRA, PRAGMA

Andy McCammon,
UCSD

Rommie Amaro, UCI

Michel Sanner, TSRI

Sriram Krishnan, SDSC

Programming Staff:

Nadya Williams,

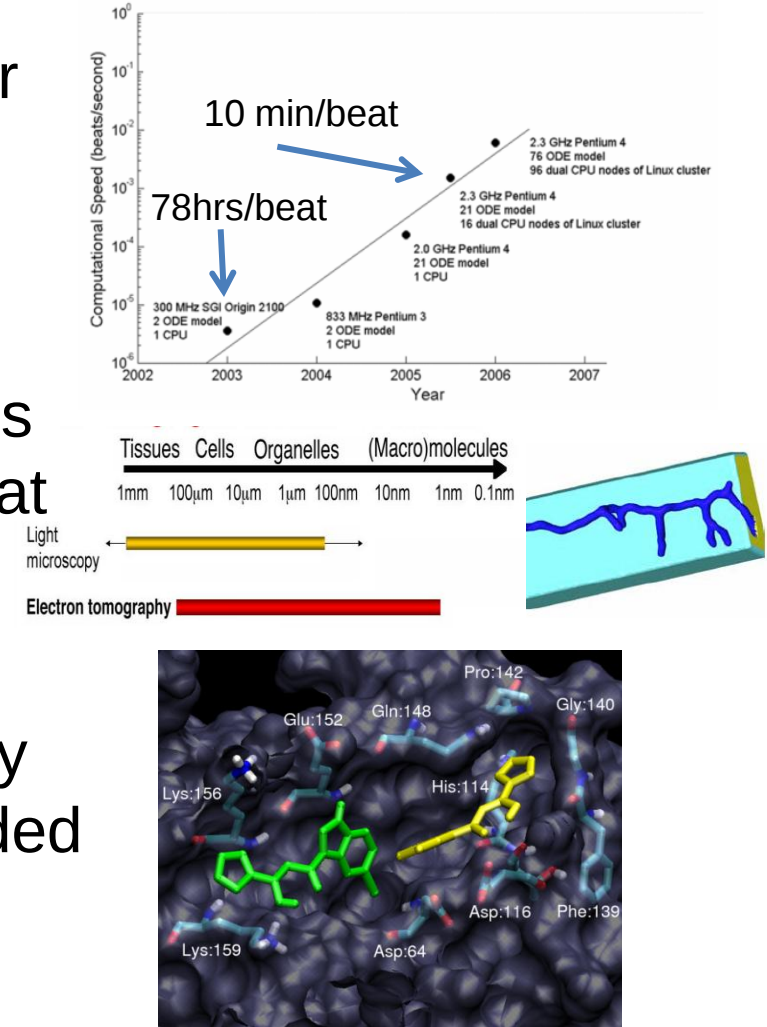
Jane Ren

<http://www.pragma-grid.net>

<http://www.nbcr.net>

Computational Translational Medical Science: Potential in the next 5 years

- Improving treatment planning for heart disease through individual patient modeling
- Understanding role of realistic subcellular structure on functions of cells via multiscale modeling at the mesoscale
- Speeding drug discovery by creating, improving the efficiency of, and enhancing computer aided drug discovery pipeline



Tools, Simulation Packages and Pipeline, CI