

The VPH initiative and its relationship with the pharmacoinformatics

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Virtual Physiological Human NoE



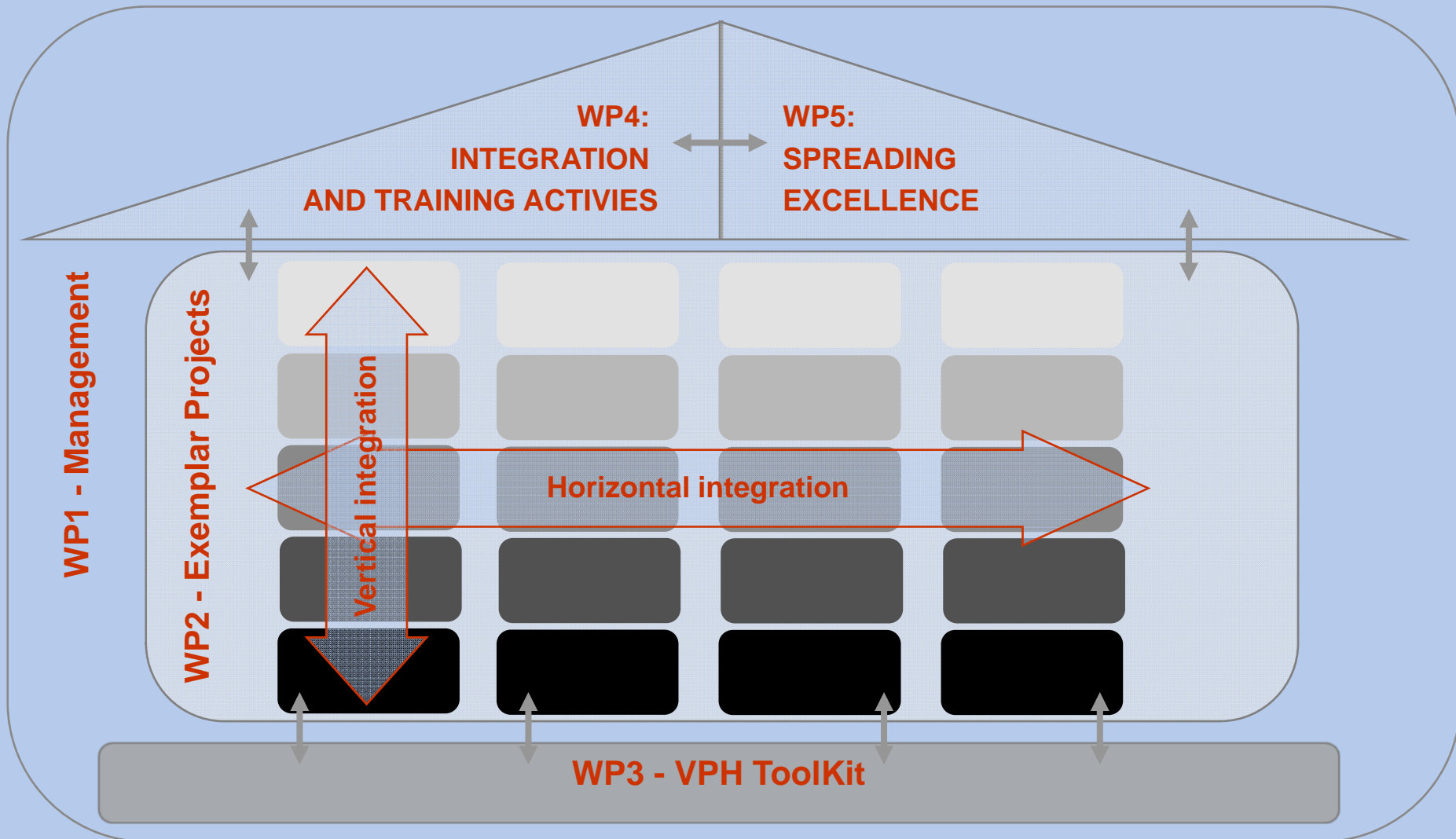
- **Coordinators: Peter Coveney (UCL), Peter Kohl (Oxford)**
- **13 Core Partners**
 - 4 UK (UCL, UOXF, UNOTT, USFD)
 - 3 France (CNRS, INRIA, ERCIM)
 - 2 Spain (UPF, IMIM)
 - 1 Germany (EMBL [EBI])
 - 1 Sweden (KI)
 - 1 Belgium (ULB)
 - 1 New Zealand (UOA)
- **Associate / General Membership**
 - 19 Candidate General Members
 - 3 Candidate Associate Members (organisations)
 - 5 Candidate Associate Members (industry)
 - 9 Associate Projects
 - ... **and growing**
- **Funding**
 - ~9.65M€ (~7.99M€ EU funding), June 2008 – December 2012
- **More information at: <http://www.vph-noe.eu>**

The VPH NoE

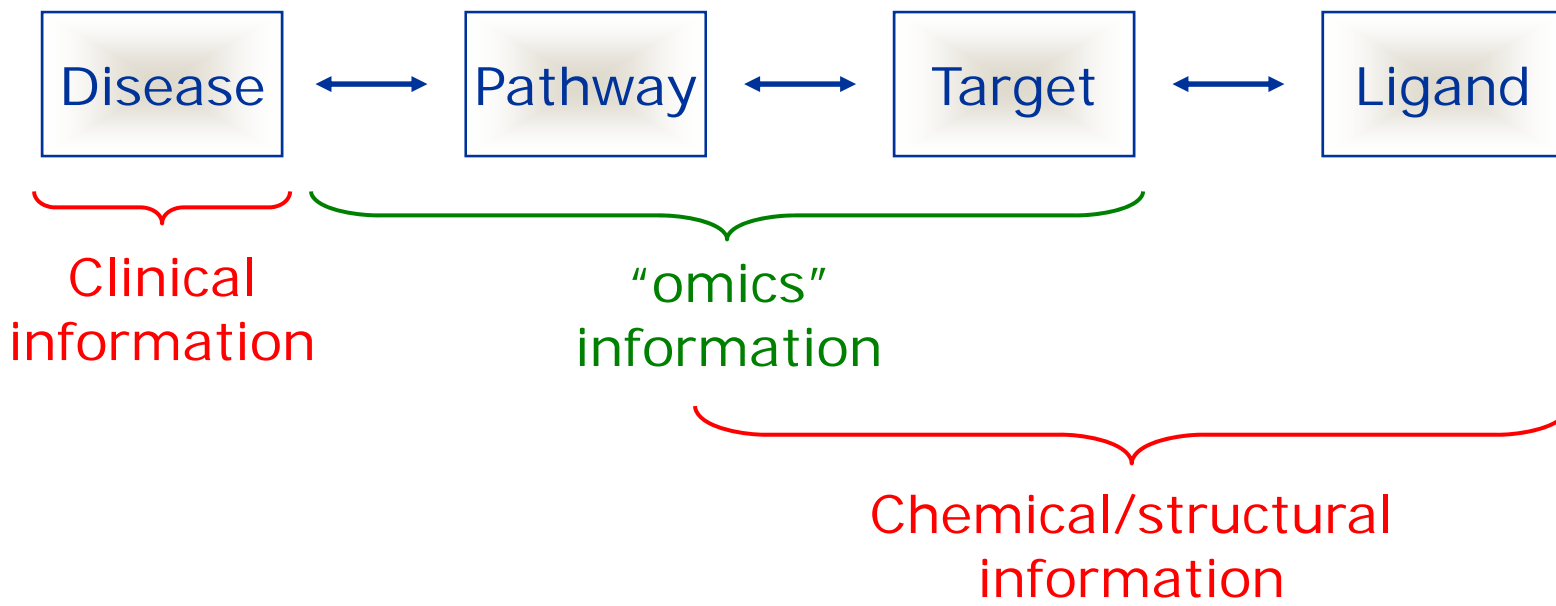
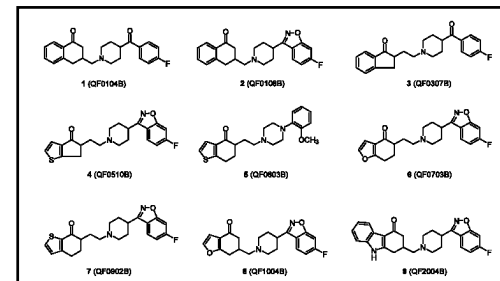
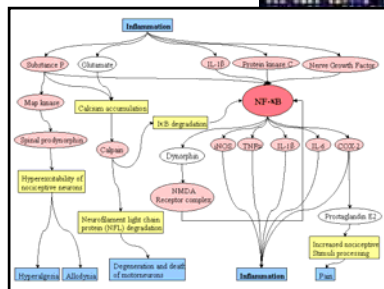


- **VPH**: framework for computational representation of the human body as an integrated, complex and dynamic system
- **NoE**: coordination of efforts, identification of user needs, standards, ontologies, toolkit, application, training, dissemination
- **Community** building
- **Long-term** sustainability

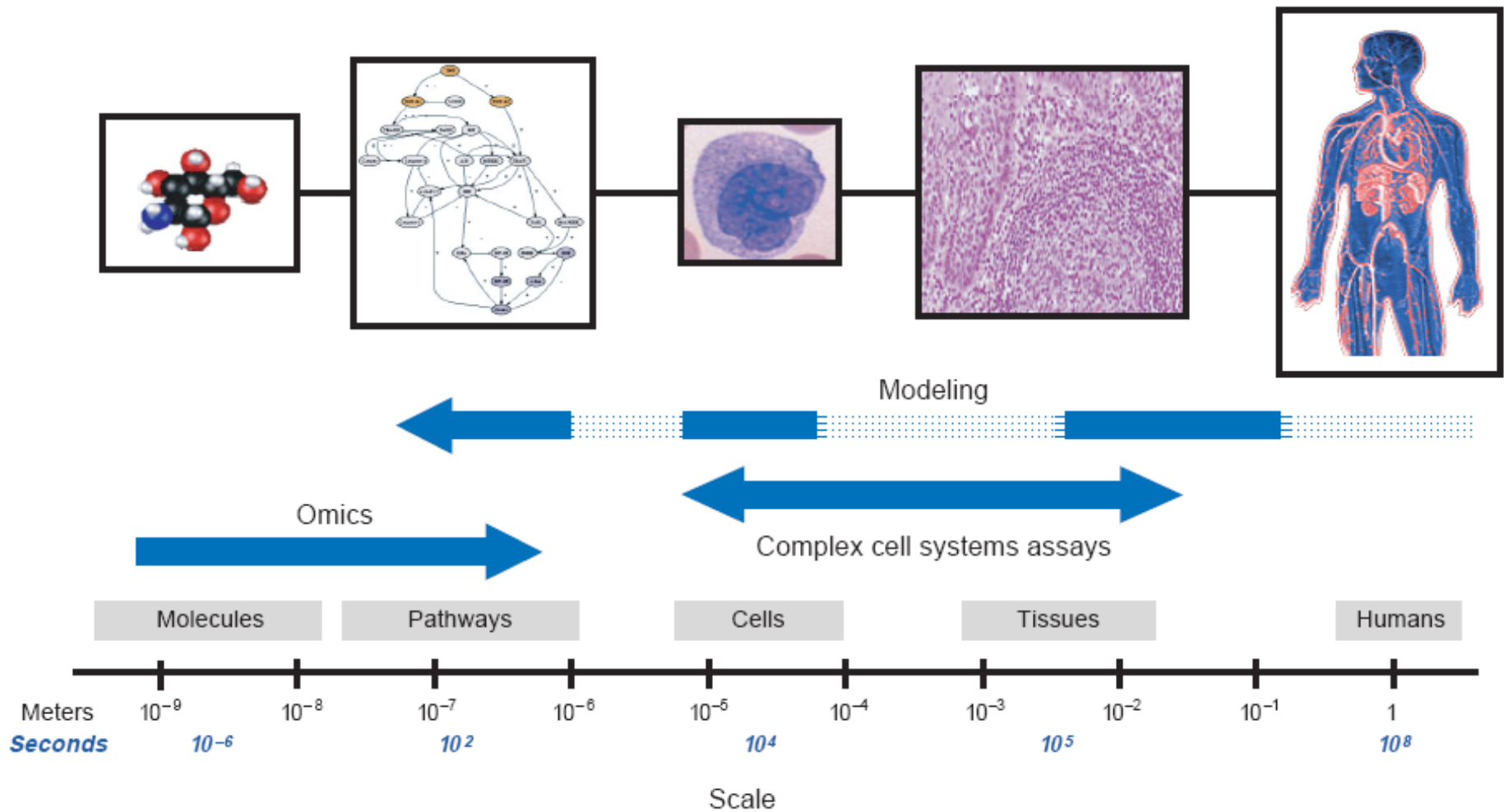
VPH NoE structure



Integration of heterogeneous biomedical information in order to gain a more complete and powerful view on diseases and therapeutics

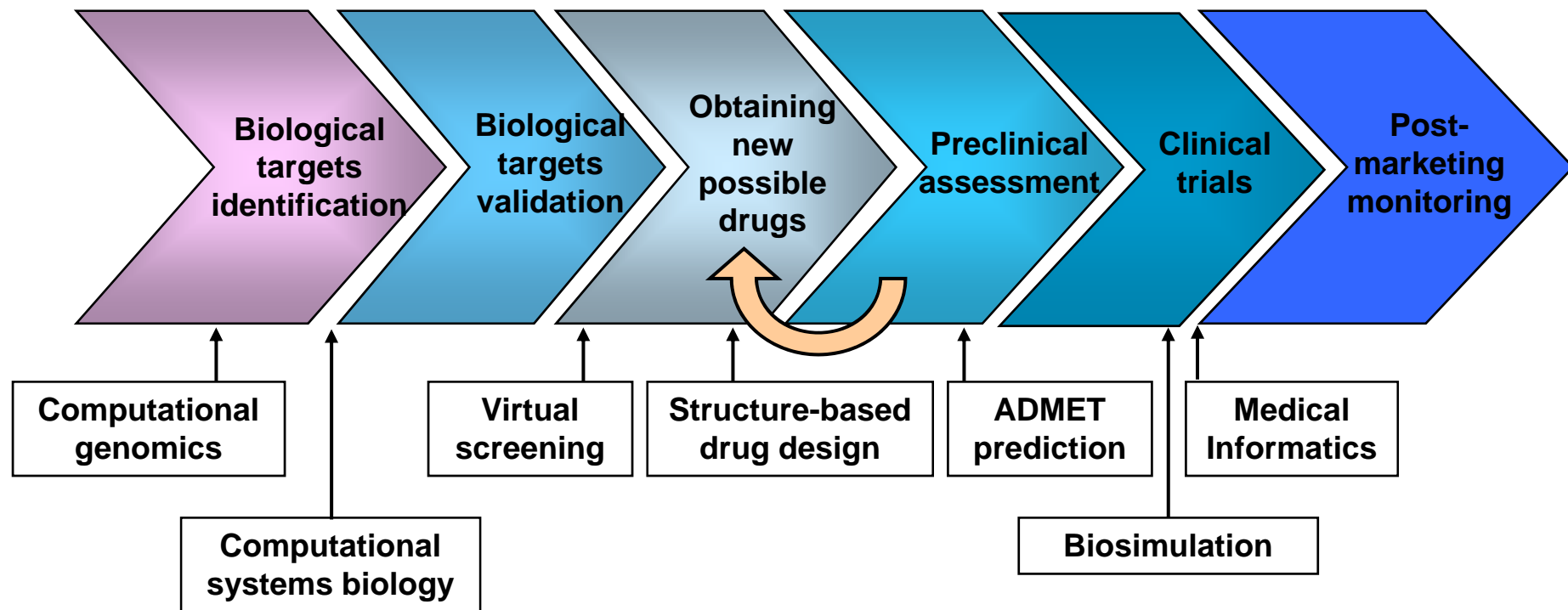


Multi-scale modeling and simulation



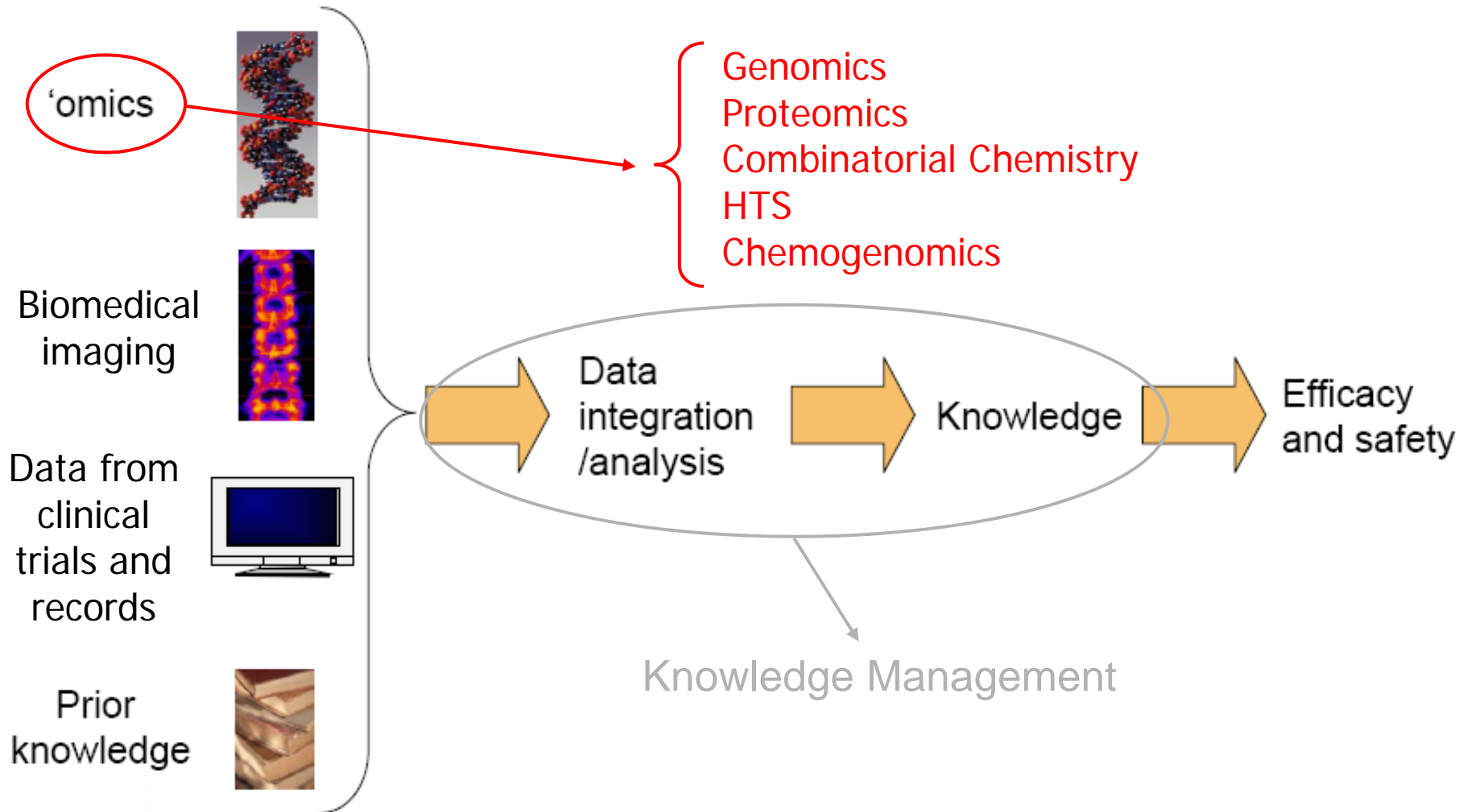
Reproduced from Butcher EC et al. Nat Biotech 2004; 22: 1253-9.

Pharmacoinformatics supporting the pharmaceutical R&D pipeline



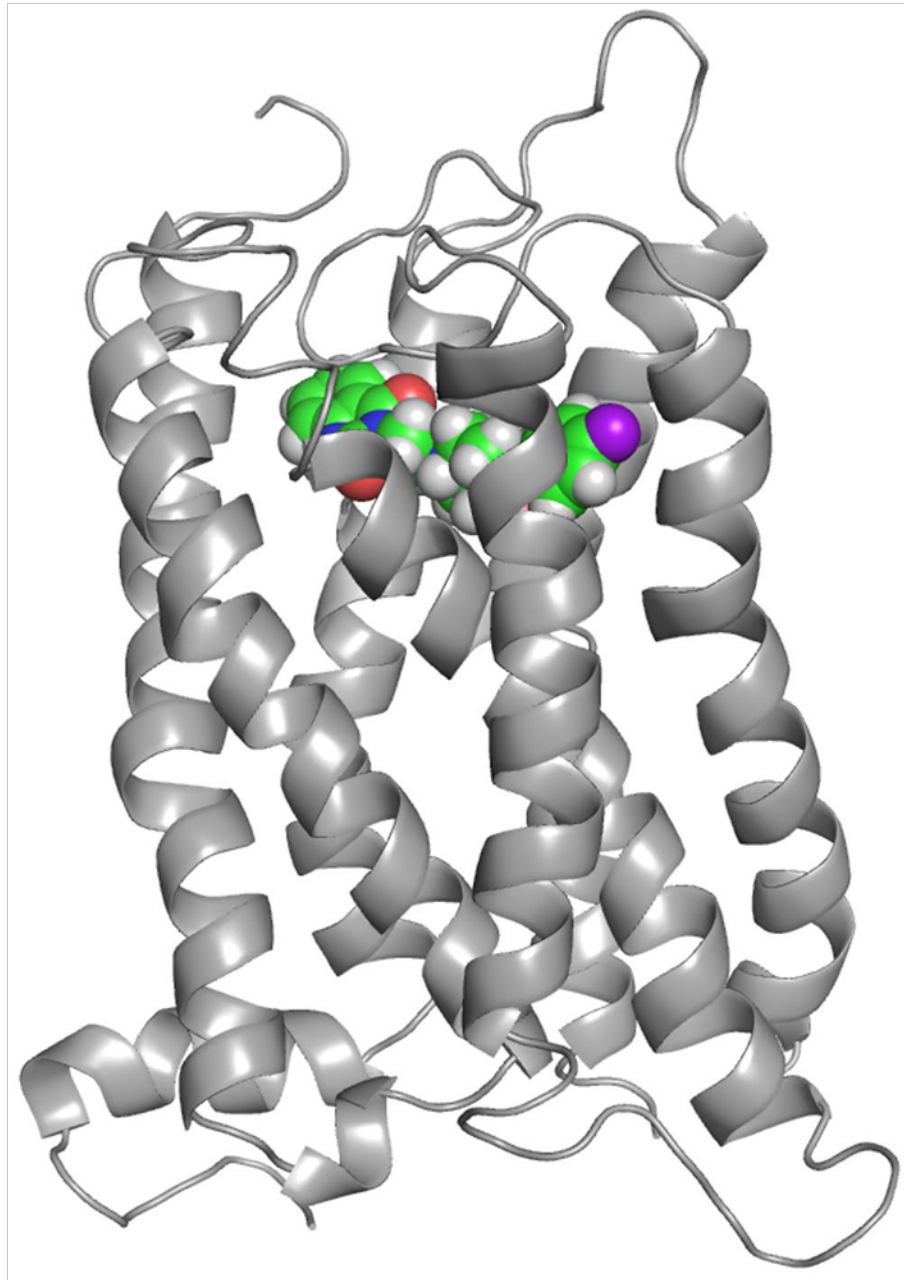
Need of integrative knowledge management and exploitation

Integrative knowledge management as envisaged in IMI

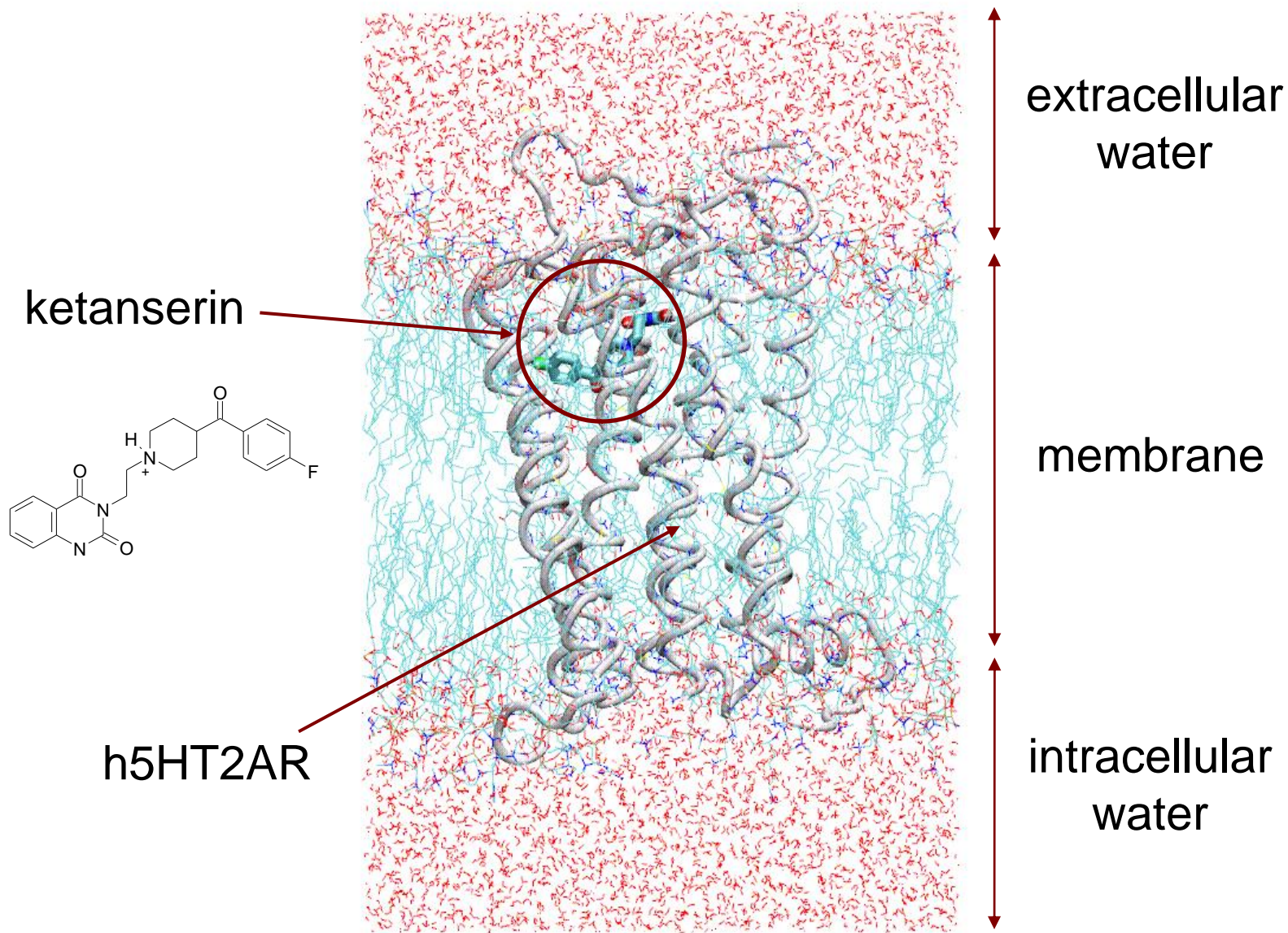


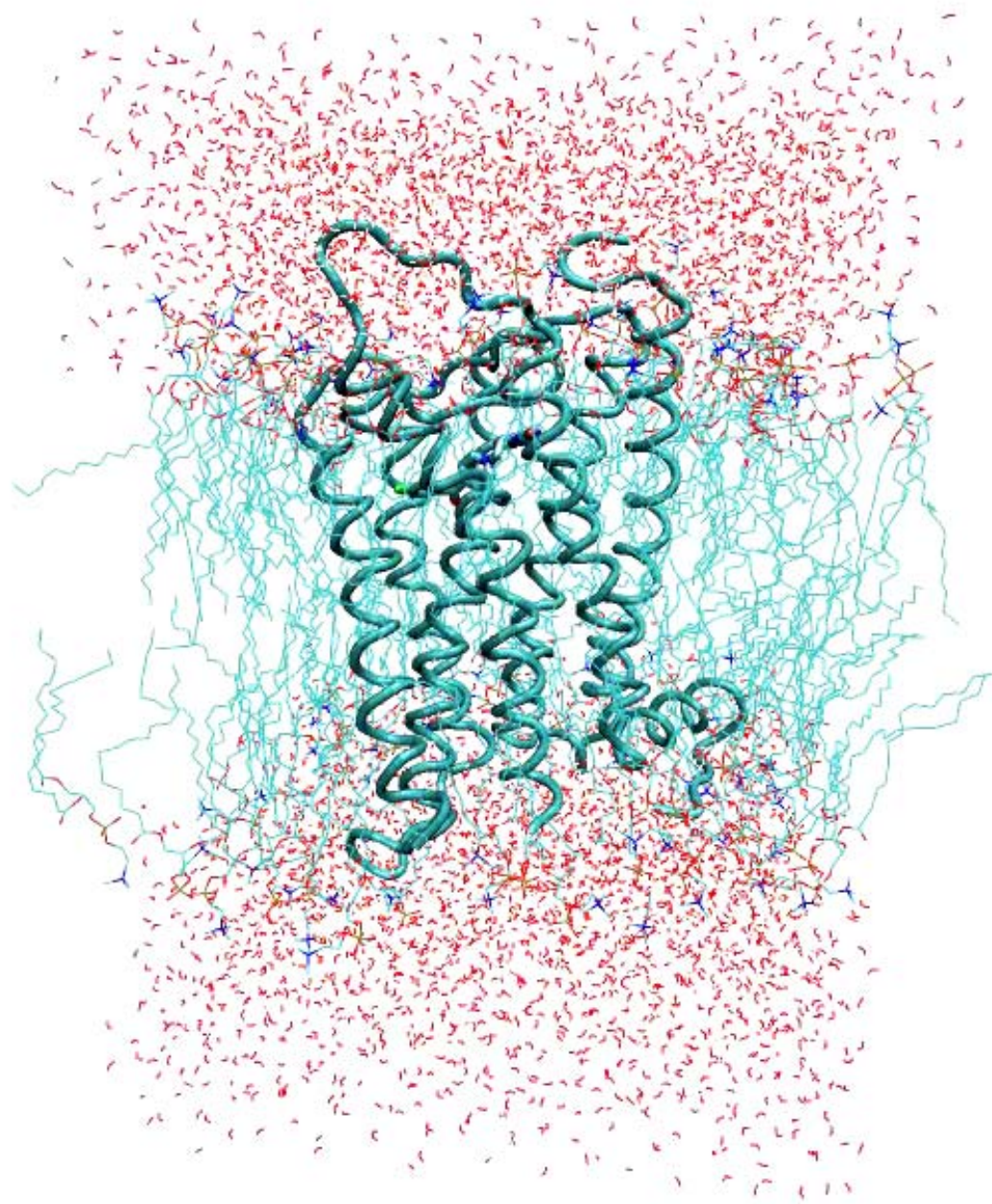
Adapted from a presentation of Ian Ragan. EFPIA. 2006.

Homology modeling of h5HT2AR and ketanserin docking

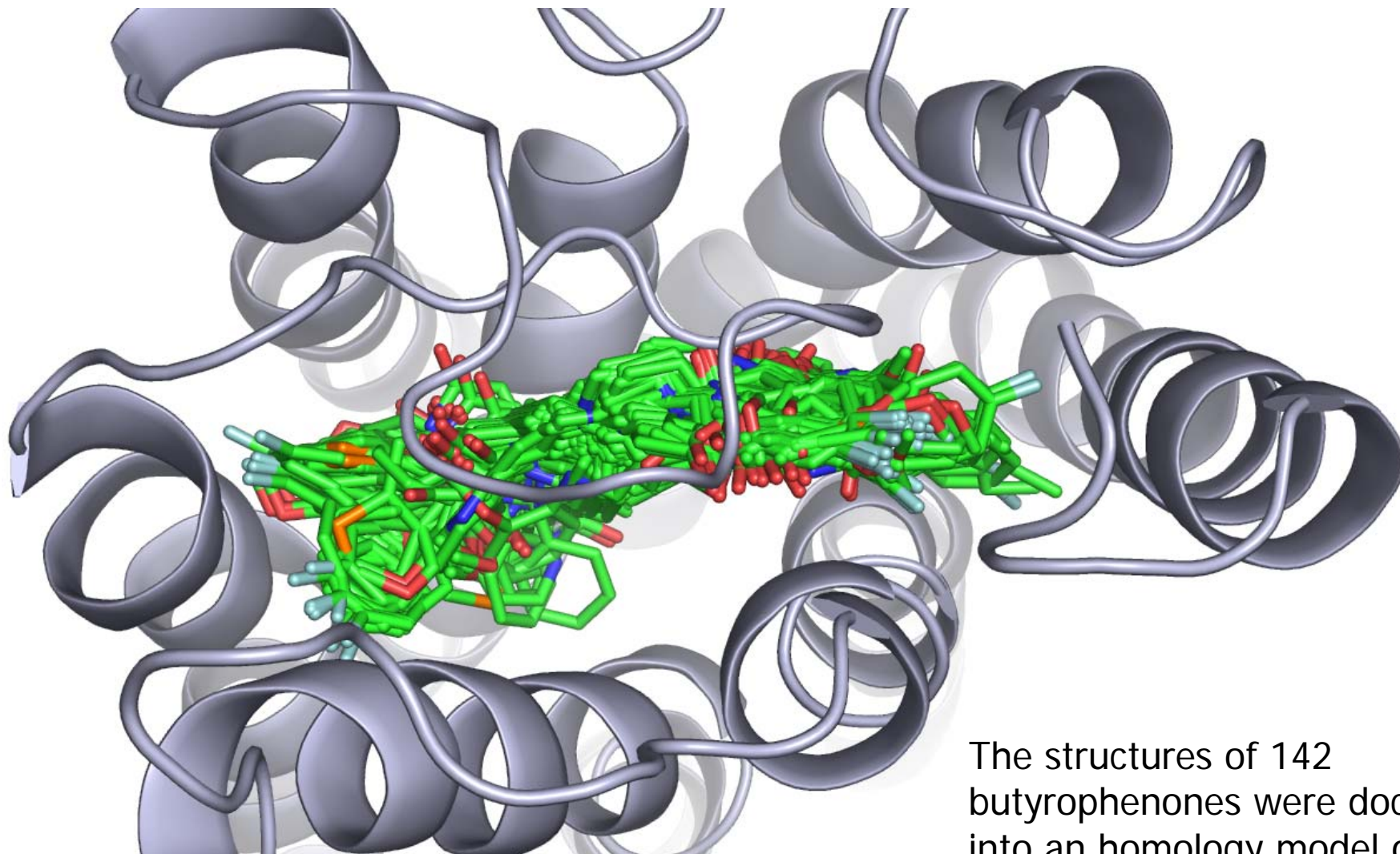


Homology modeling of h5HT2AR and ketanserin docking



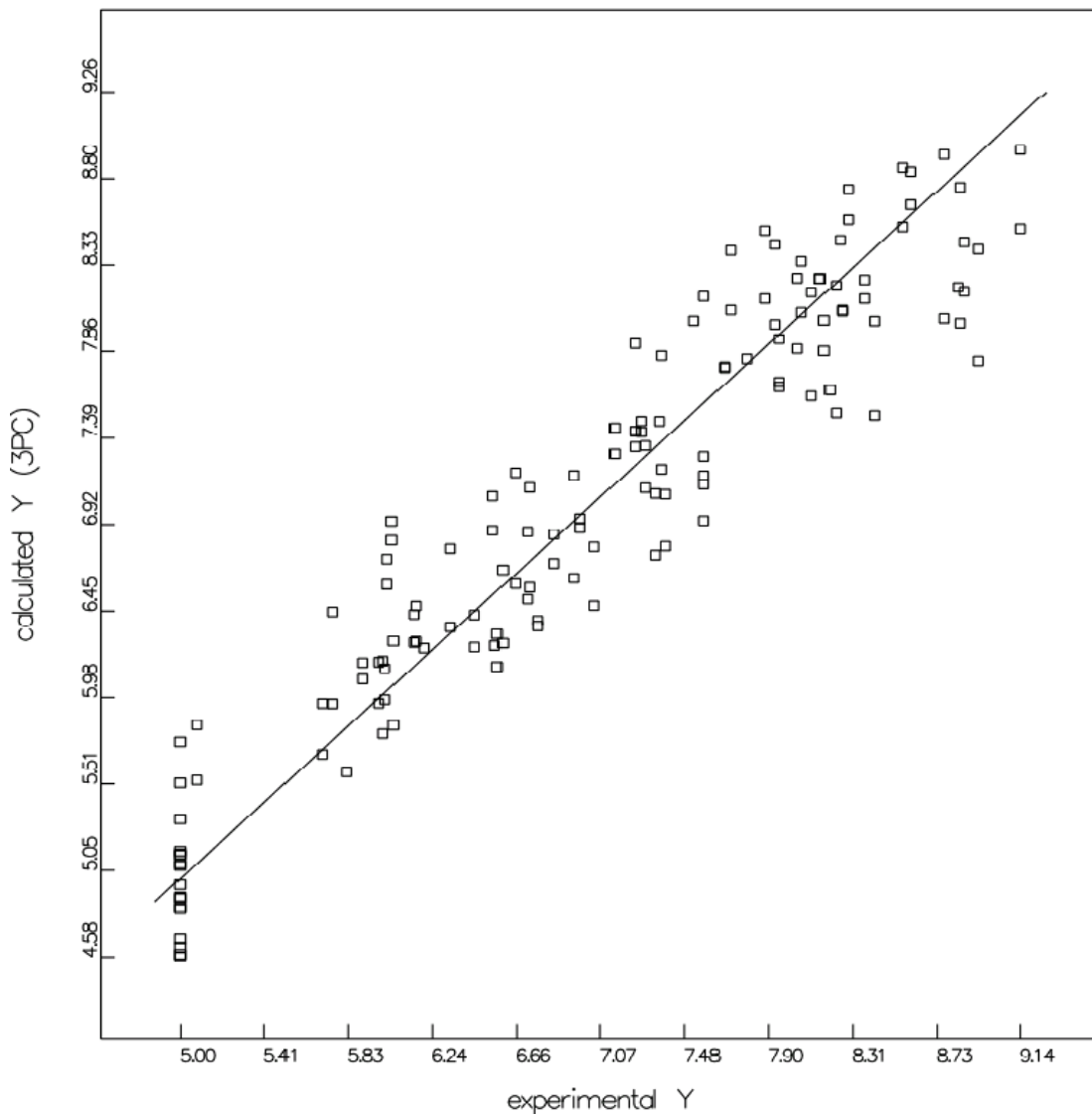


Docking of the USC butyrophenones in the h5HT_{2A}R model



The structures of 142 butyrophenones were docked into an homology model of the receptor using GOLD \Rightarrow "bioactive alignment"

3D-QSAR modeling using GRID/GOLPE and the “bioactive alignment” of the compounds.



n=142

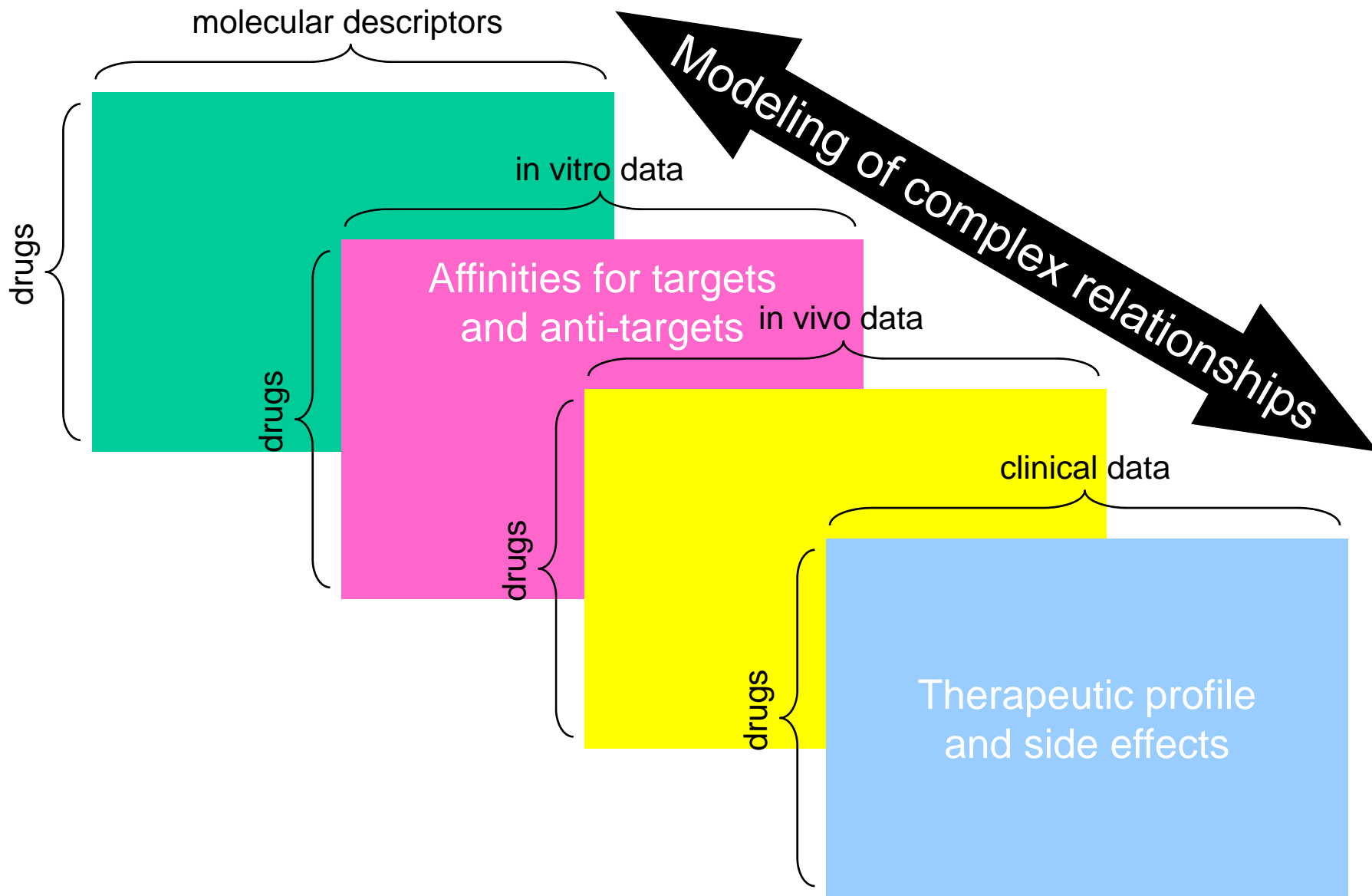
3 probes (DRY, O, N1)

3 latent variables

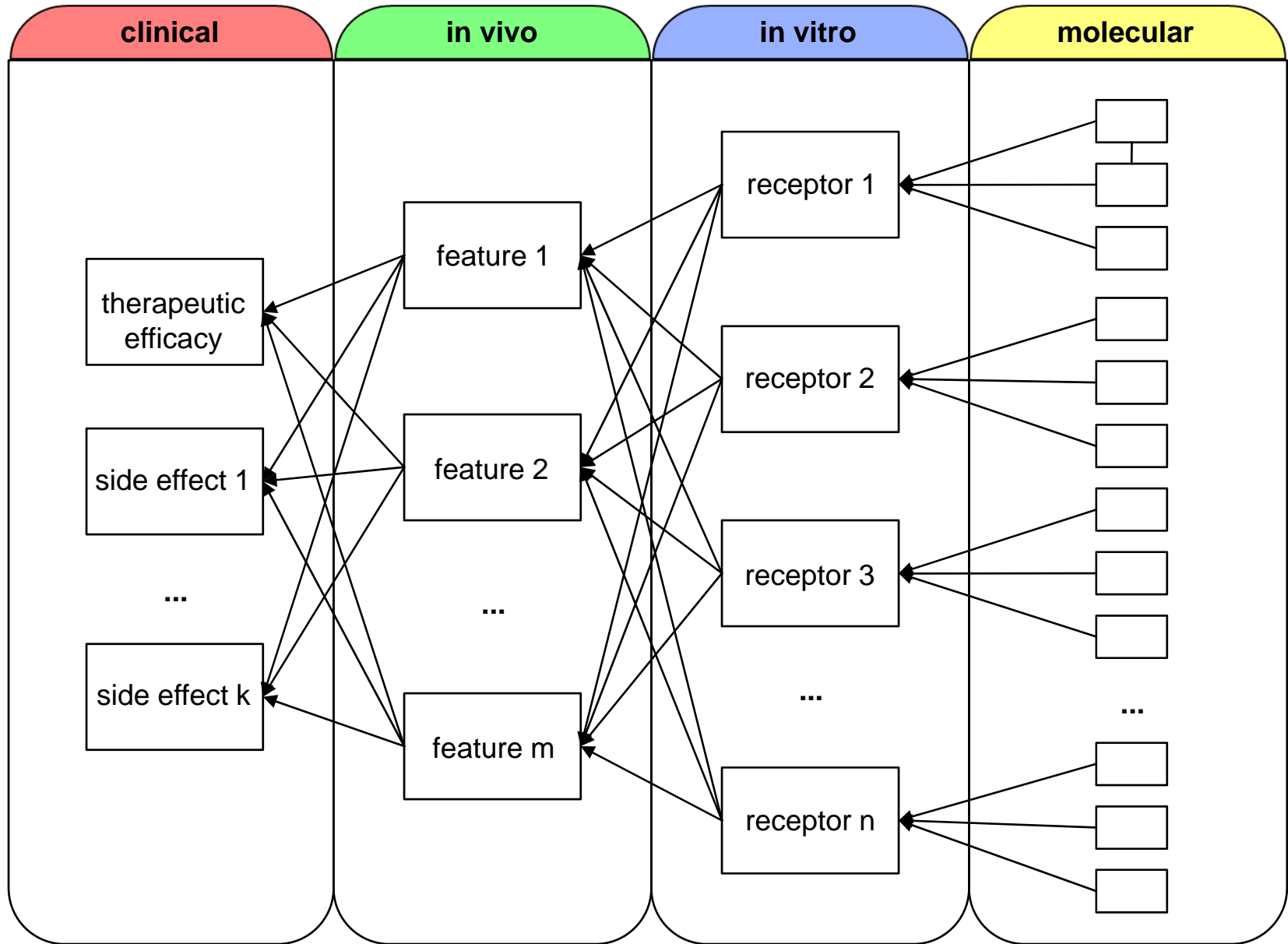
$r^2=0.90$; $q^2=0.78$

External validation (10% of the compounds selected by the Most Descriptive Compound algorithm and reserved for validation):
SDEP=0.53 ; $r^2=0.80$

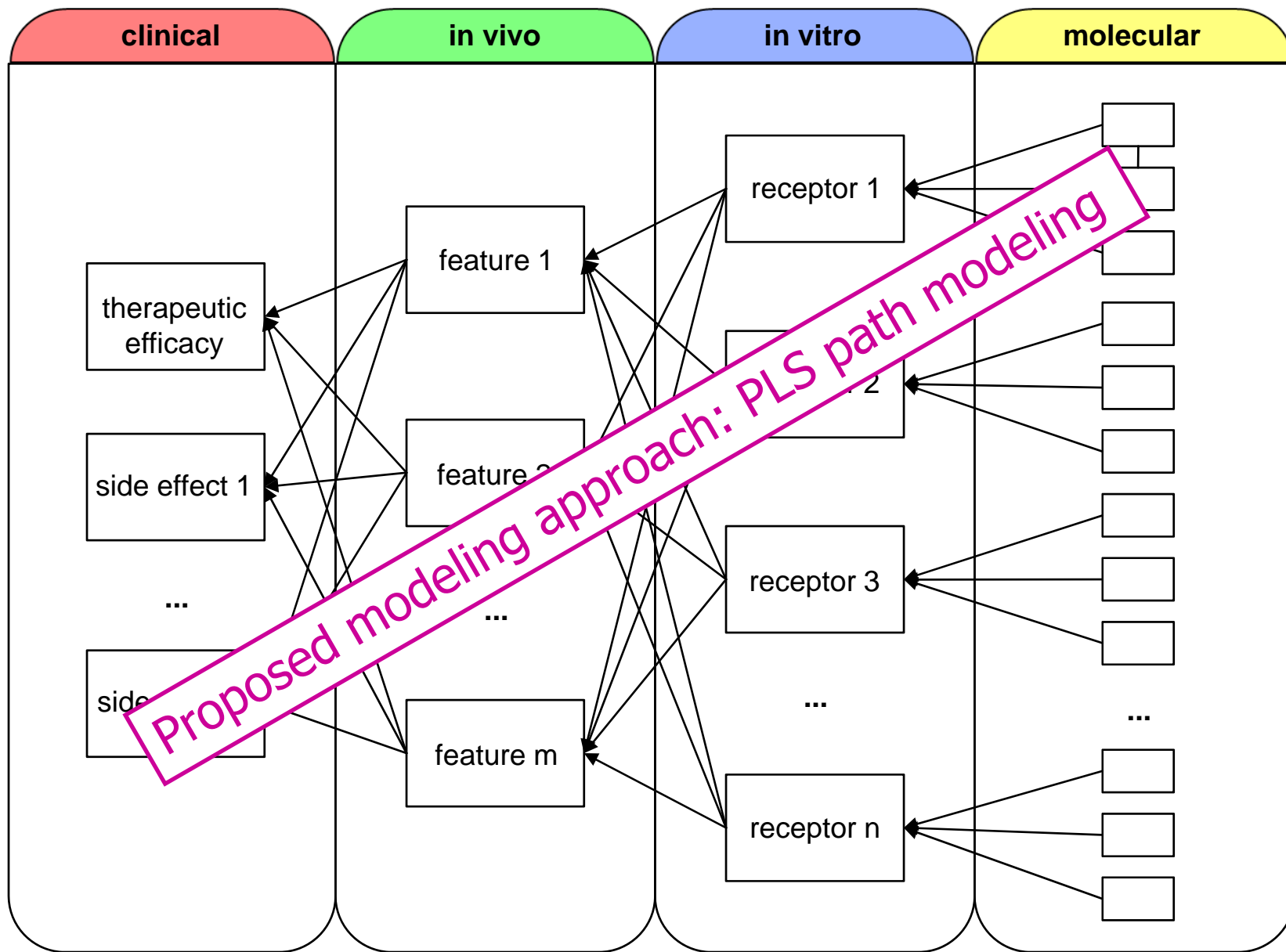
The envisaged modeling in pharmacoinformatics



The envisaged modeling in pharmacoinformatics



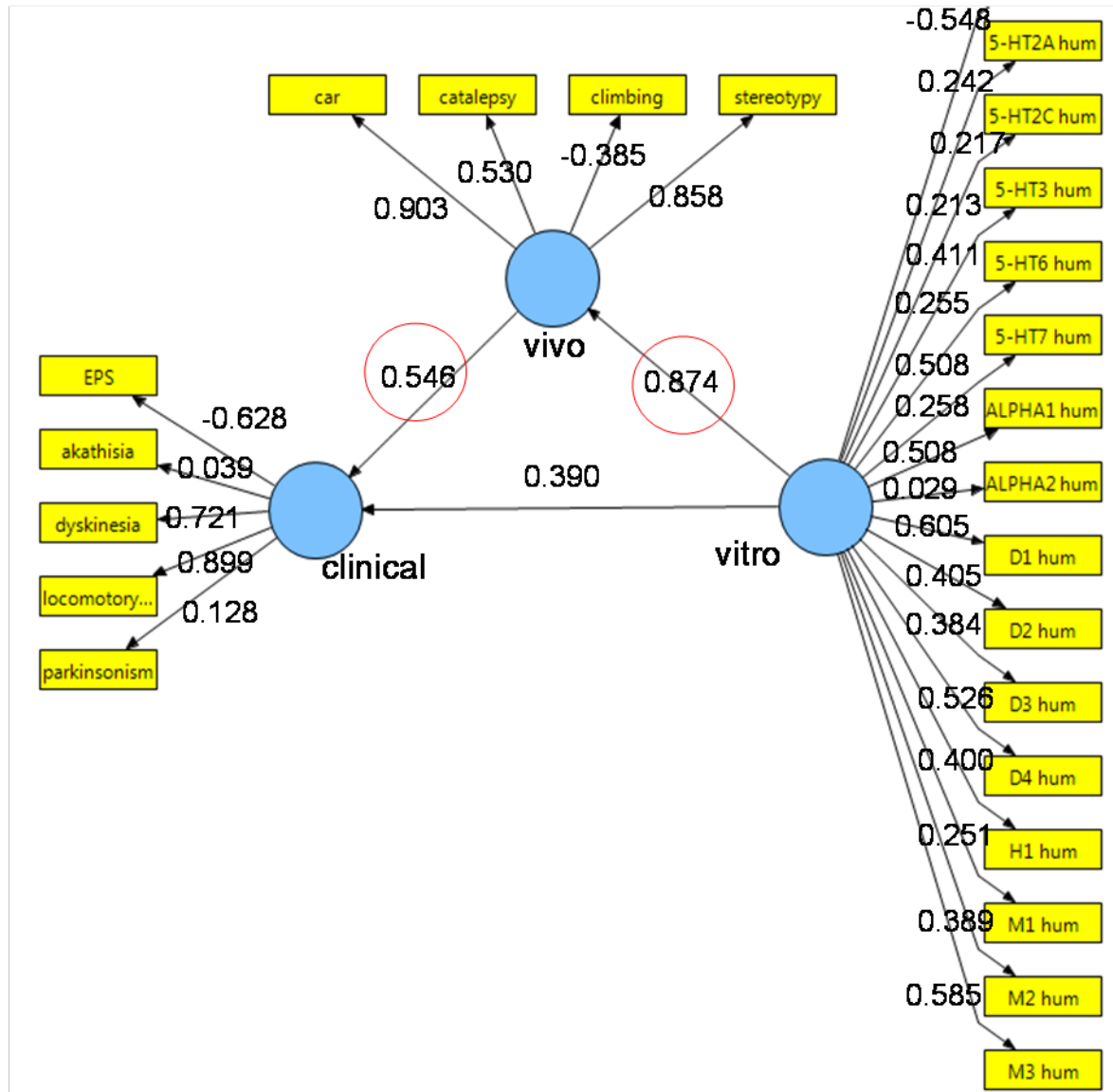
The envisaged modeling in pharmacoinformatics



Data matrix (fragment)

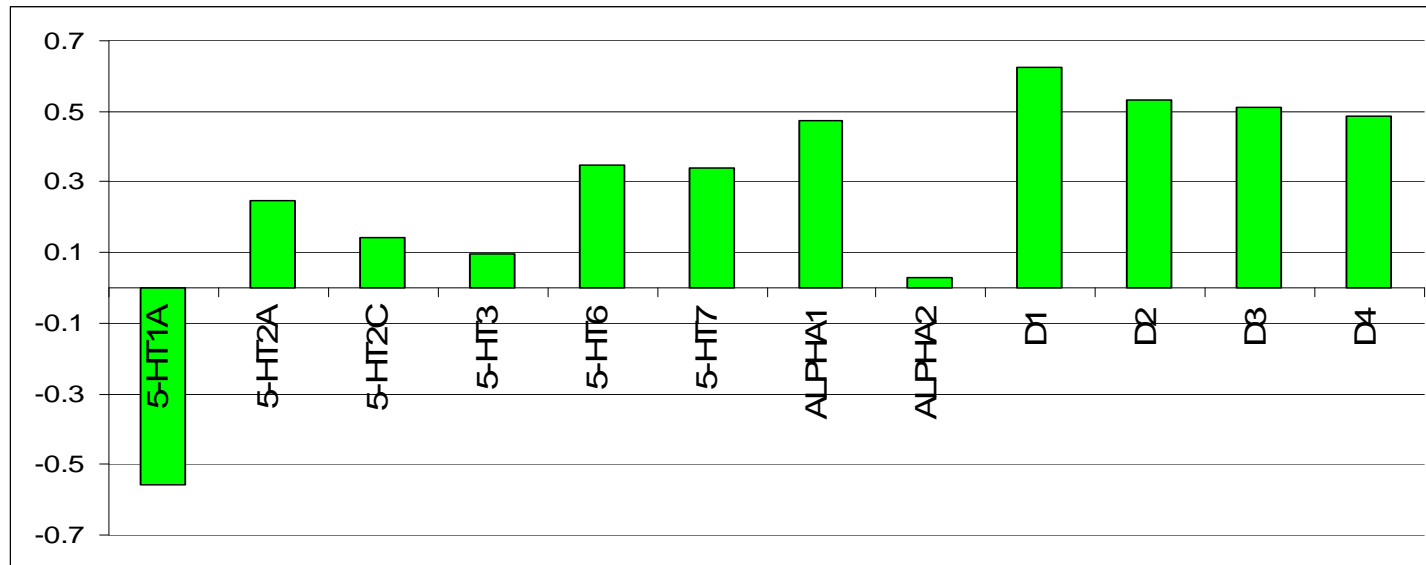
drug	5-HT1A hum	D1 hum	H1 hum	M1 hum	climbing	cataplexia	movement	d tremor	akathisia
aripiprazole	2.63218331	-1.09669656	-0.35000321	-0.91199971	-0.47359426	-0.59766602			-0.02328378
chlorpromazine	-0.62563672	0.08111161	0.3023905	0.58758068	-0.06048382	0.29384406	1.36859512	-0.434819245	-1.13889986
clozapine	0.38045476	-0.00506948	1.58781383	1.33002	-1.24004302	-1.2472461	-1.4659666		
fluphenazine	-0.52981848	0.94292246	-0.23383373	-0.67677141	1.50912327	1.49147069	1.22793689	0.53750513	1.08438566
haloperidol	-0.67354584	0.48329001	-1.0558093	-0.66206964	0.89969305	1.3521267		0.168734961	0.65106243
loxapine	-0.84122775	0.52159271	0.55542633	0.39645769	1.62603882	1.4099866			0.70836648
molindone	-0.80529591	-1.6425101	-1.22950965	-2.10284296		0.01771282		1.985804696	0.78508599
olanzapine	-0.61365944	0.73225759	2.04887518	1.27856381	-0.88994228	0.84140889	-0.53142128	0.113935601	1.35954197
perphezine	-0.68552312	0.66522785	0.3023905	-0.47094665		0.65474824	1.90955	-0.857081638	
pimozide	0.16486373	-1.52760198	-0.96087936		0.44647962	0.06502948		0.528143163	1.25388747
quetiapine	0.28463652	-0.69451816	0.00622962	0.33029973	-0.40226811	-0.62506636	-0.53142128		-1.74757747
risperidone	0.18881829	-0.11997759	-0.03122738	-0.90464883	0.57033498	1.14175345	-0.16891373	-1.61747001	-0.33780774
sertindole	0.21277285	0.808863	-0.91575522	-0.15485863	0.86792892	-1.04035323	-0.53142128	-1.145241795	-0.76591371
sulpiride	-1.52393268	-1.77656956	-1.23135275		-1.56012744	-1.48649309	0.31732601		
thioridazine	0.50022756	0.37795757	-0.13708612	1.30796734	-0.67480316	-0.59766602	-0.53142128	-0.049805993	-0.56921622
ziprasidone	1.66202367	1.57491709	-0.27411573	-0.32392897	-0.61833658	-0.64331932	-0.53142128	0.77029513	-0.04170344
zotepine	0.27265925	0.67480353	1.61644649	0.97717755		-1.0302708	-0.53142128		-1.21792777

PLS path modeling results



Loadings of the in vitro variables for catalepsy

Key influence of
dopamine receptors



Acknowledgements:

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VPH; @neurIST; ALERT; INB; COMBIOMED*

