JÜLICH
FORSCHUNGSZENTRUM

Multiscale simulations of neuronal receptors

Institute for Advanced Simulation
Institute for Neuroscience and Medicine (IAS-5/INM-9/INM-1)
Computational Medicine
Juelich Research Center, Germany
Physics Department, RWTH-Aachen University,
Aachen, Germany

July 3,, 2017| Paolo Carloni

Forschungszentrum Jülich (Jülich Research Centre)

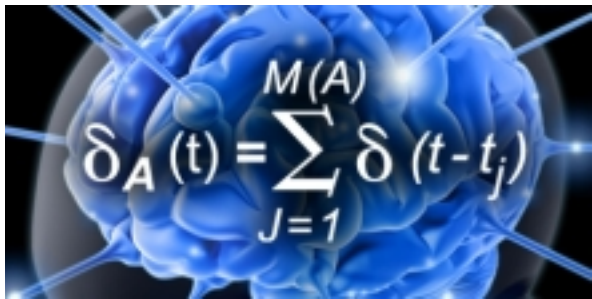
JÜLICH FORSCHUNGSZENTRUM

Interdisciplinary research center, among the largest in Europe, focusing on the study and applications in the areas of health, neurobiology, information, environment, and energy

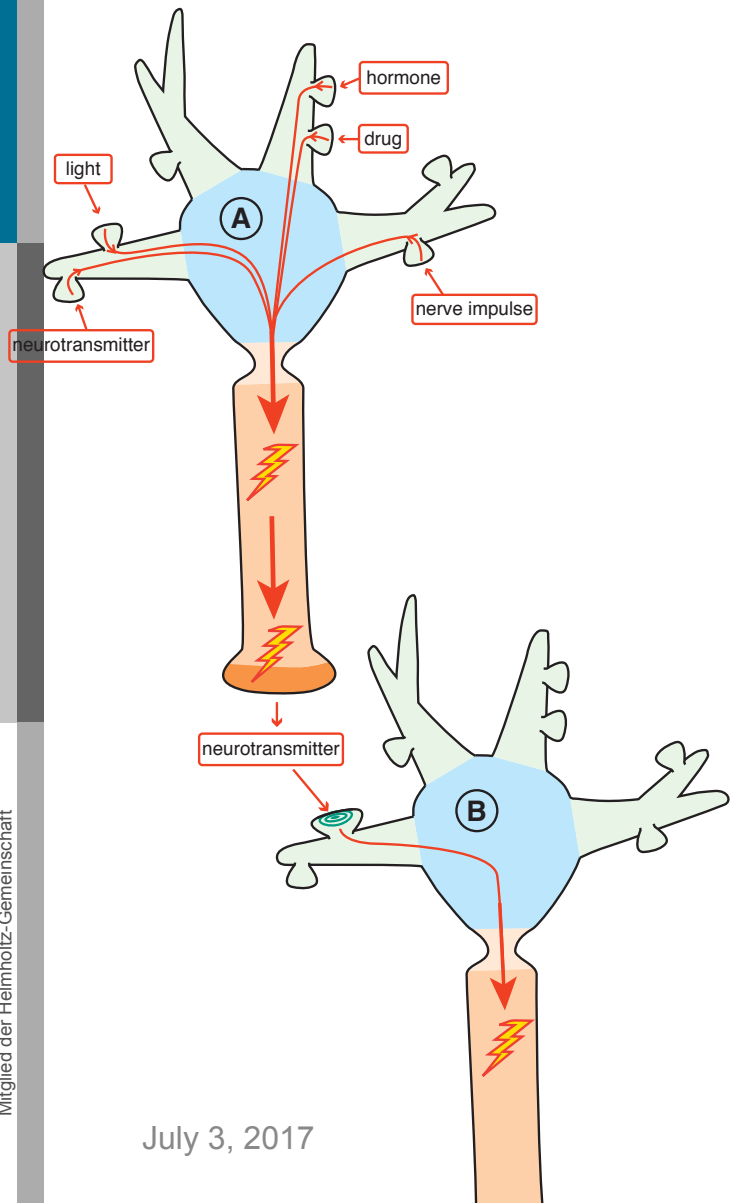
About 1500 scientists (600 PhD‘s)

Mitglied der Helmholtz-Gemeinschaft

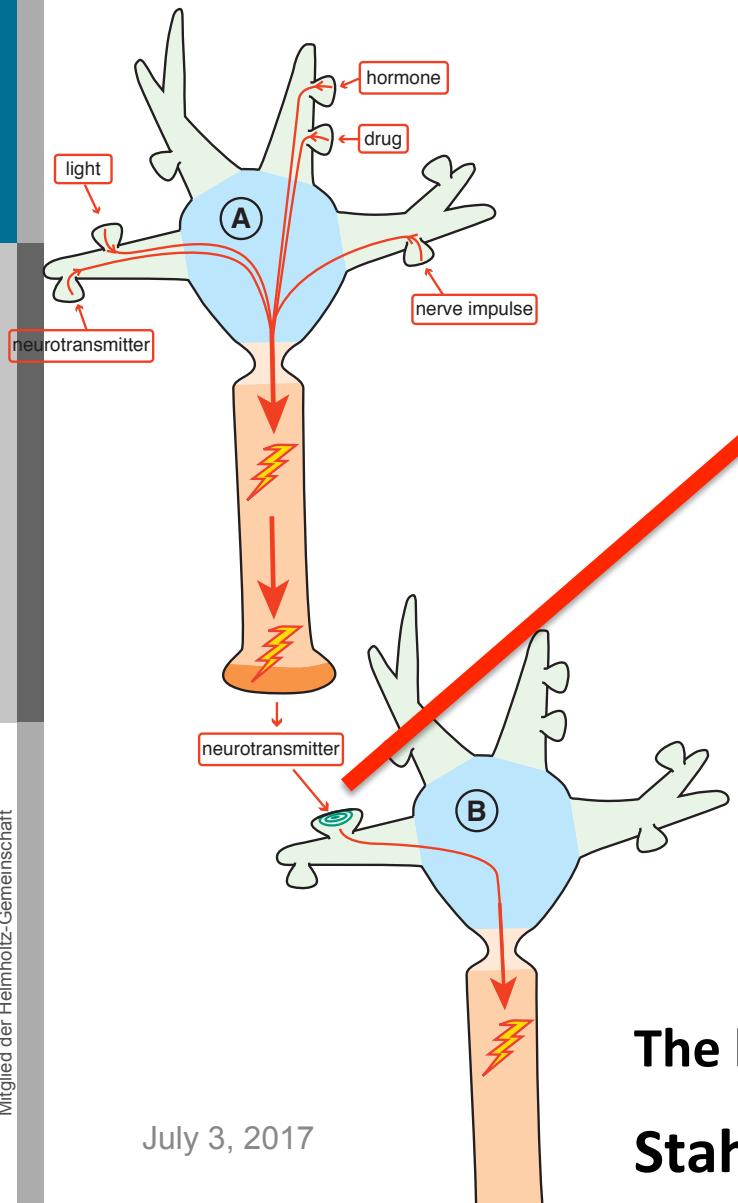
HELMHOLTZ GEMEINSCHAFT

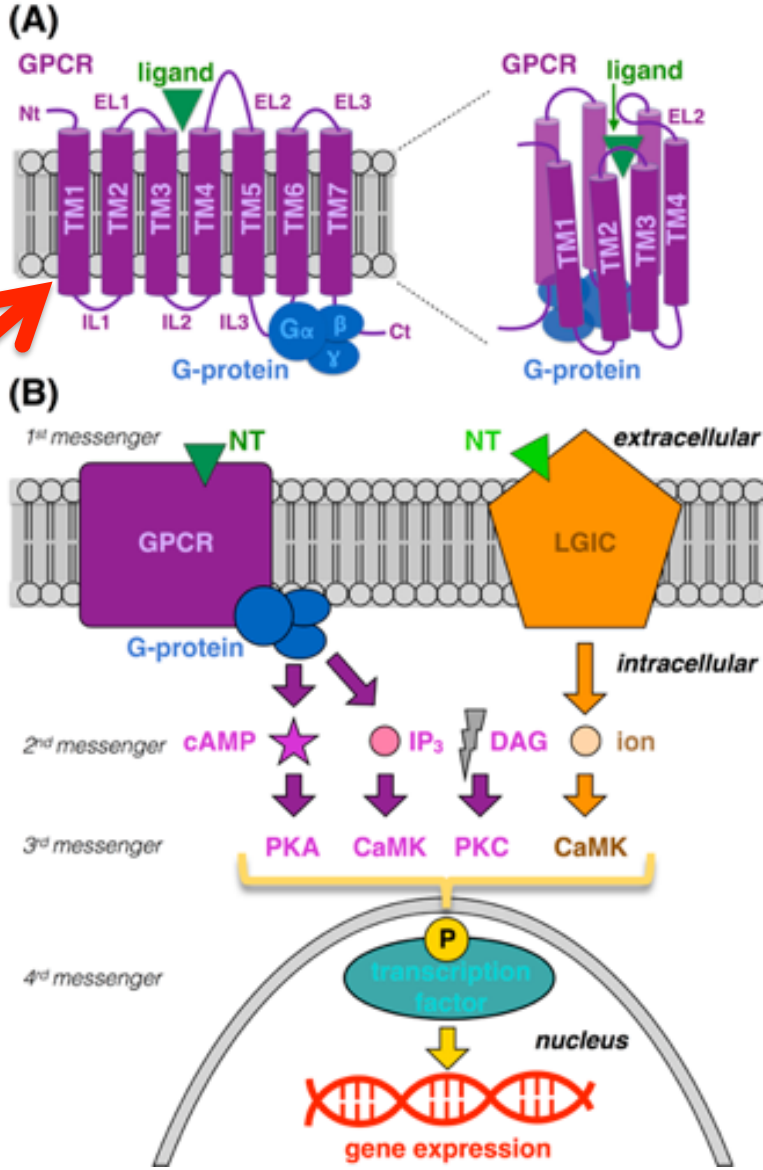


Synaptic Neurotransmission



Synaptic Neurotransmission: G-protein coupled Receptors





The brain as sophisticated "chemical soup"

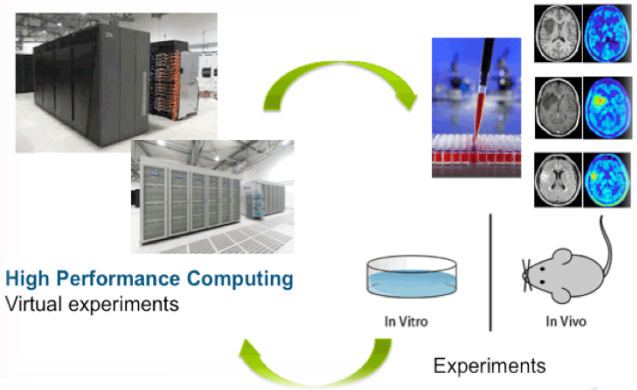
Stahl, Essential Psychopharmacology, 2013

Computational biomedicine group

JÜLICH FORSCHUNGSZENTRUM

Strategy

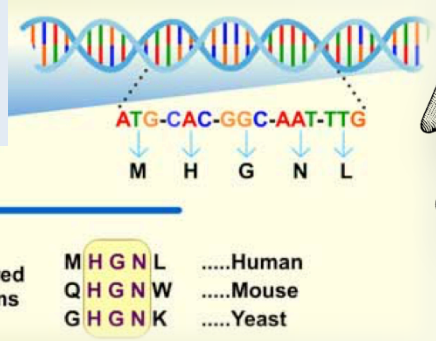
- **Key Molecular events for neuronal function/dysfunction**
- **Designing ligands**



Tools

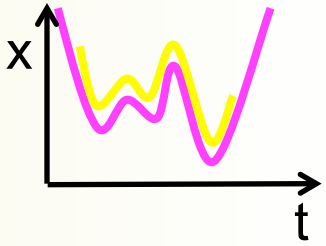
Biology-based approaches

From DNA to proteins



Physics-based approaches

$$m_i \frac{d^2}{dt^2}\vec{r}_i = -\frac{\partial}{\partial \vec{r}_i} U(\vec{r}_1, \vec{r}_2, \ldots, \vec{r}_N)$$



Statistical Mechanics

$$A = -RT \ln Q$$

binding affinities
rate constants

Supercomputing

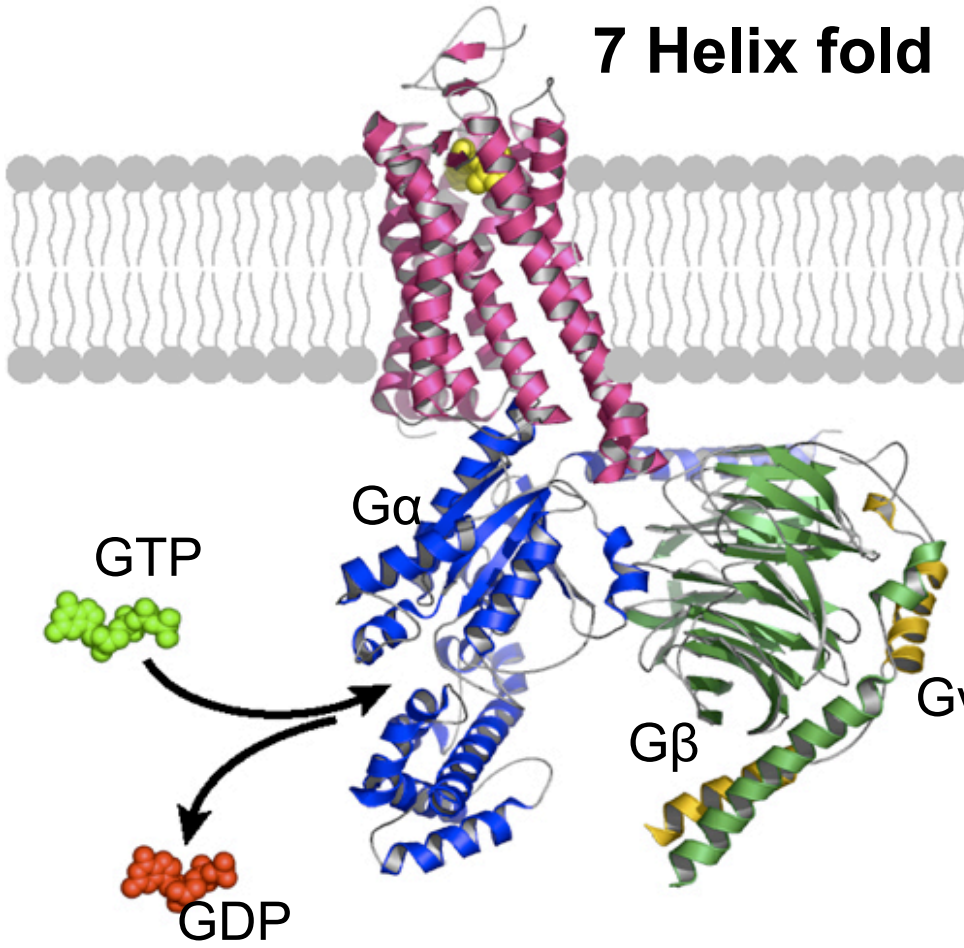
highly scalable codes for molecular simulation

G-protein Coupled Receptors (GPCRs)

~3%
of mammalian genes

~80%
signal transduction pathway
across cell membrane

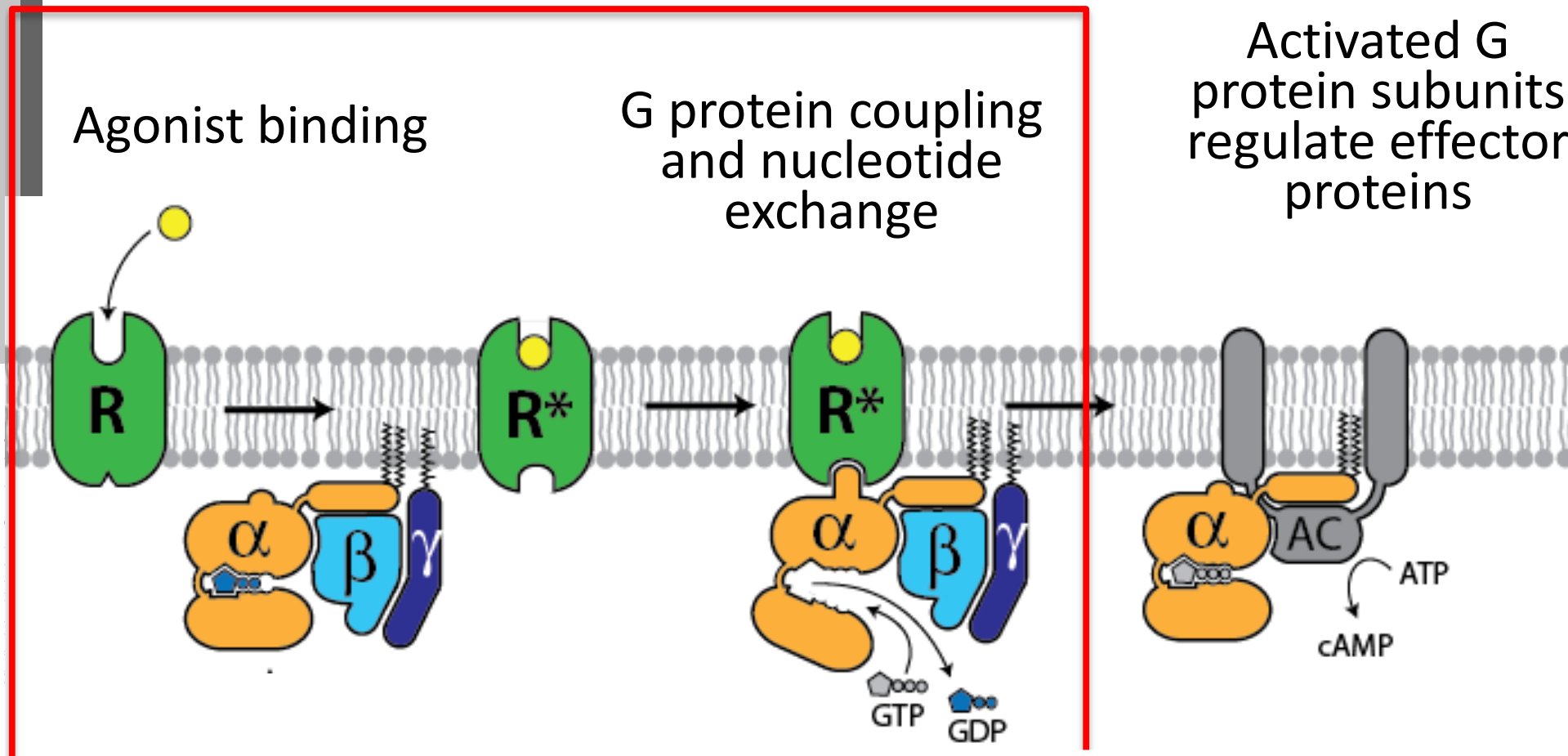
> 30 %
of marketed drugs



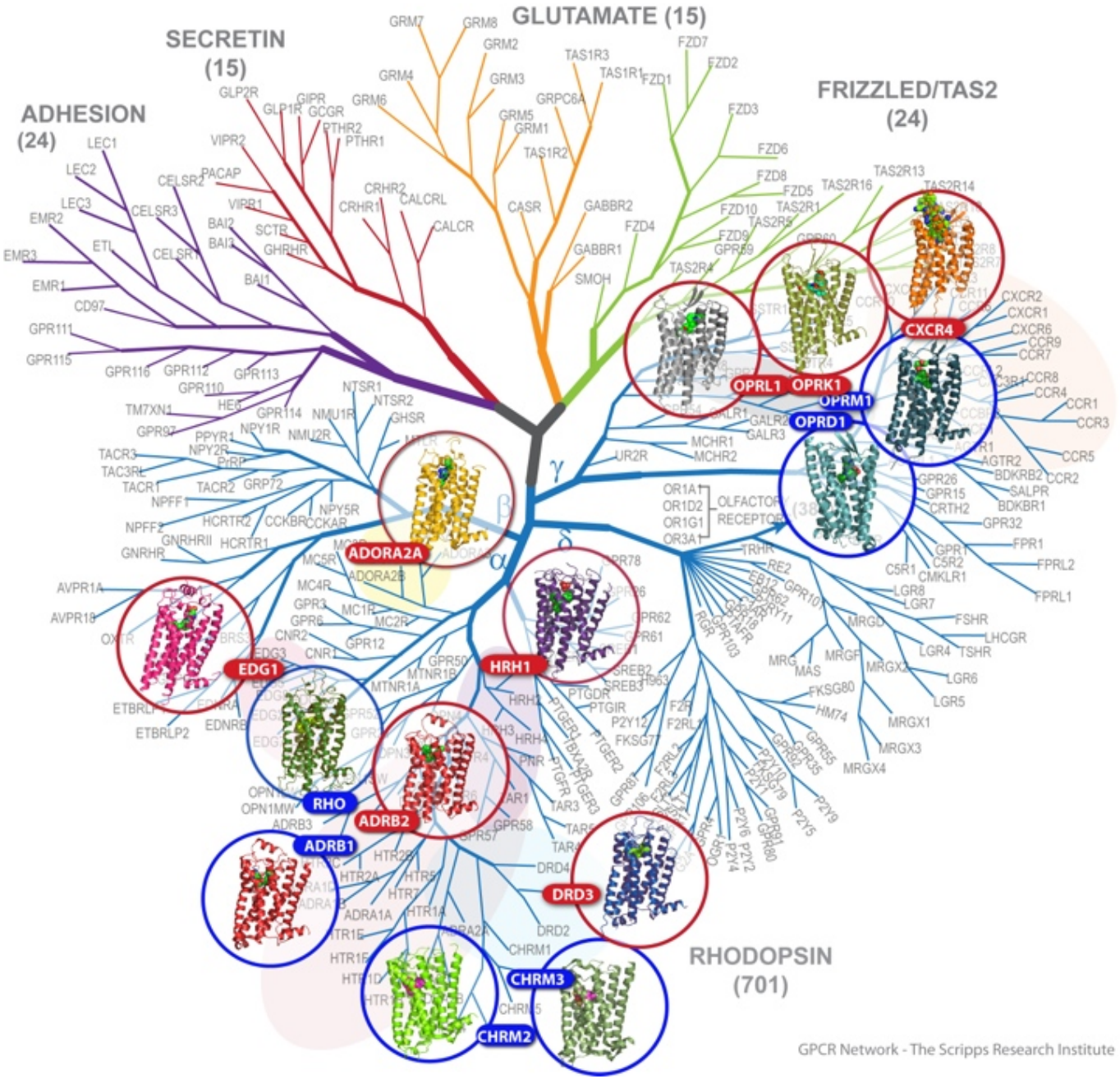
Overington et al.
Nat. Rev. Drug. Discov. 2006

Nobel Prize in Chemistry 2012
Brian Kobilka (shared with Robert J. Lefkowitz) for structural studies on GPCRs

G-protein Coupled Receptors (GPCRs)

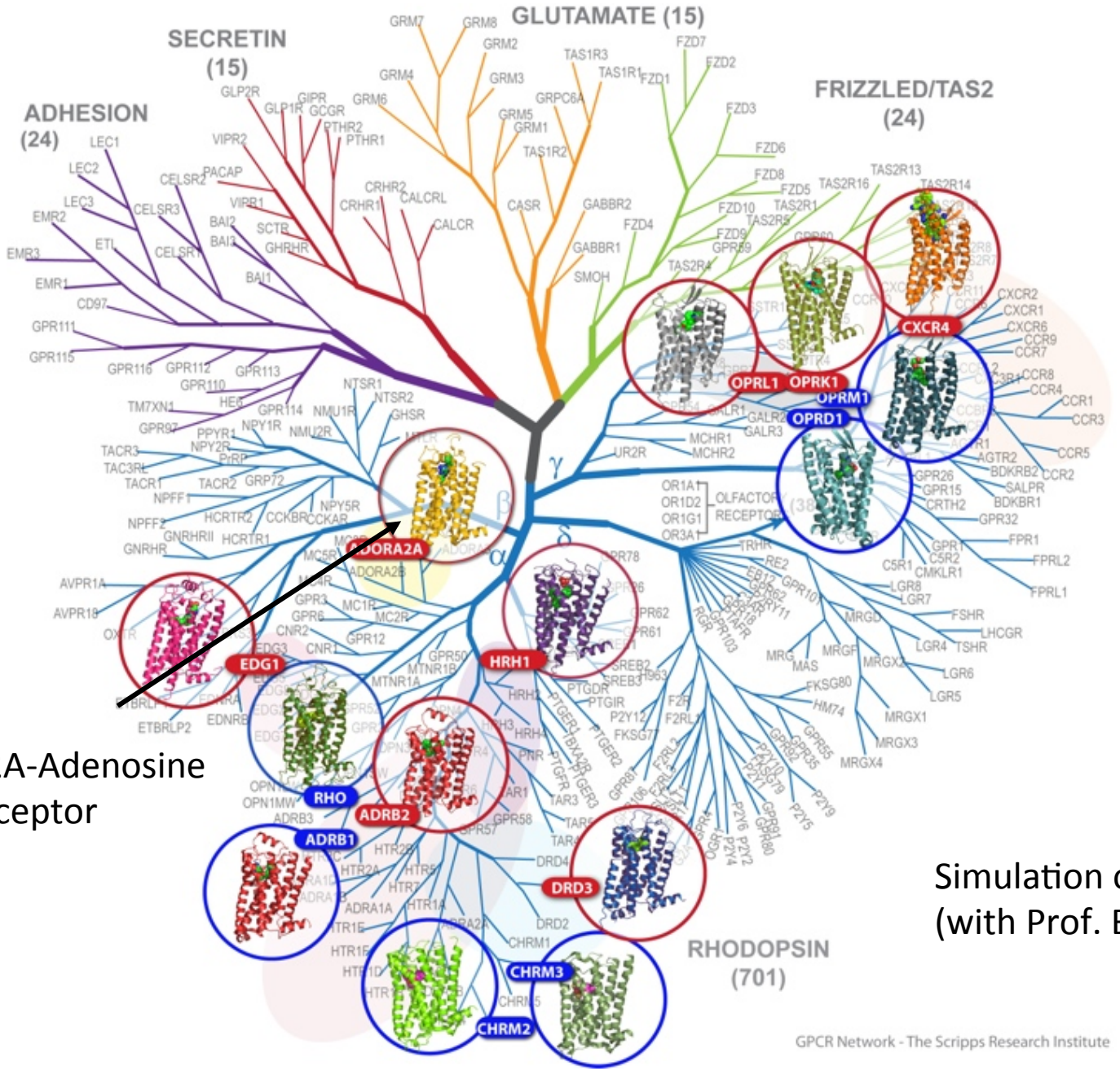


GPCR structural biology



~800 members in the human genome.

GPCR structural biology

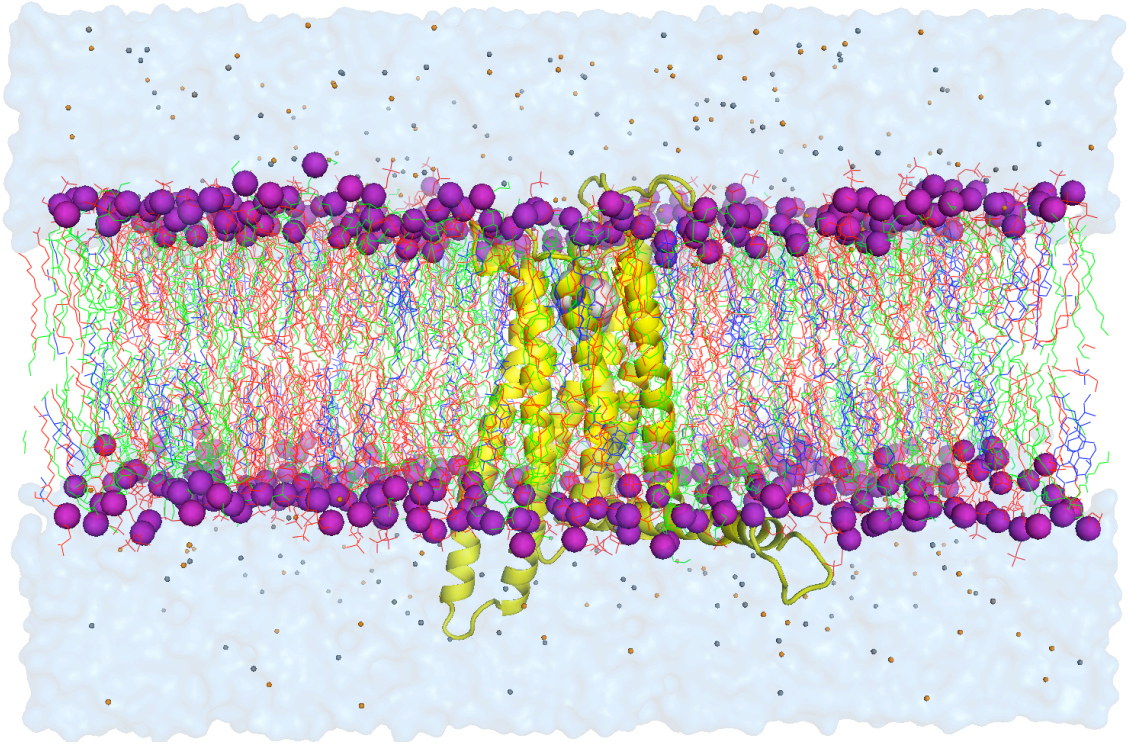


A2A-Adenosine receptor

~800 members in the human genome.

Simulation of igand binding (with Prof. Bauer, FZJ)

Molecular dynamics Simulations on The $hA_{2A}R$ neuronal receptor

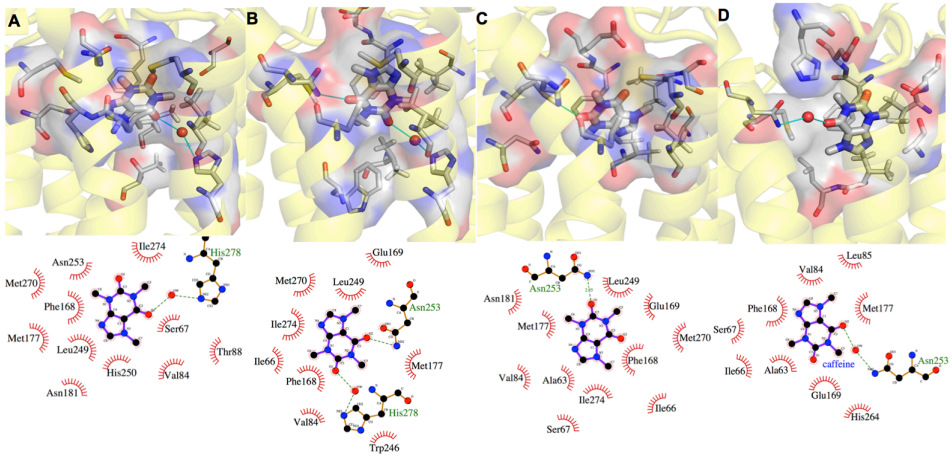


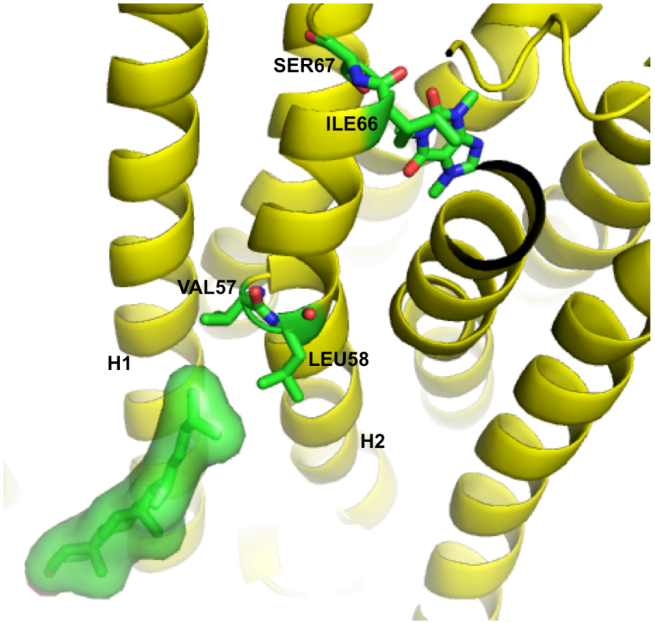
Giulia Rossetti (INM-9/JSC - W1 Aachen)
Ruiin Cao, with Prof. Bauer (INM-2)
and Neumeier (INM-5)

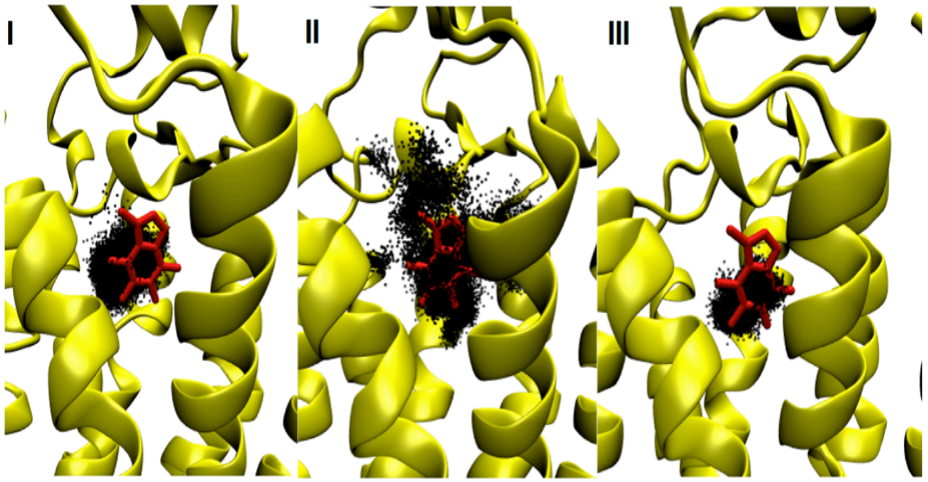
Cholesterol 33-50%
Pfrieger, *Biochimica et Biophysica Acta*

PDBid: 3PWH
Amber force field
Microsecond MD

Effect of cholesterol







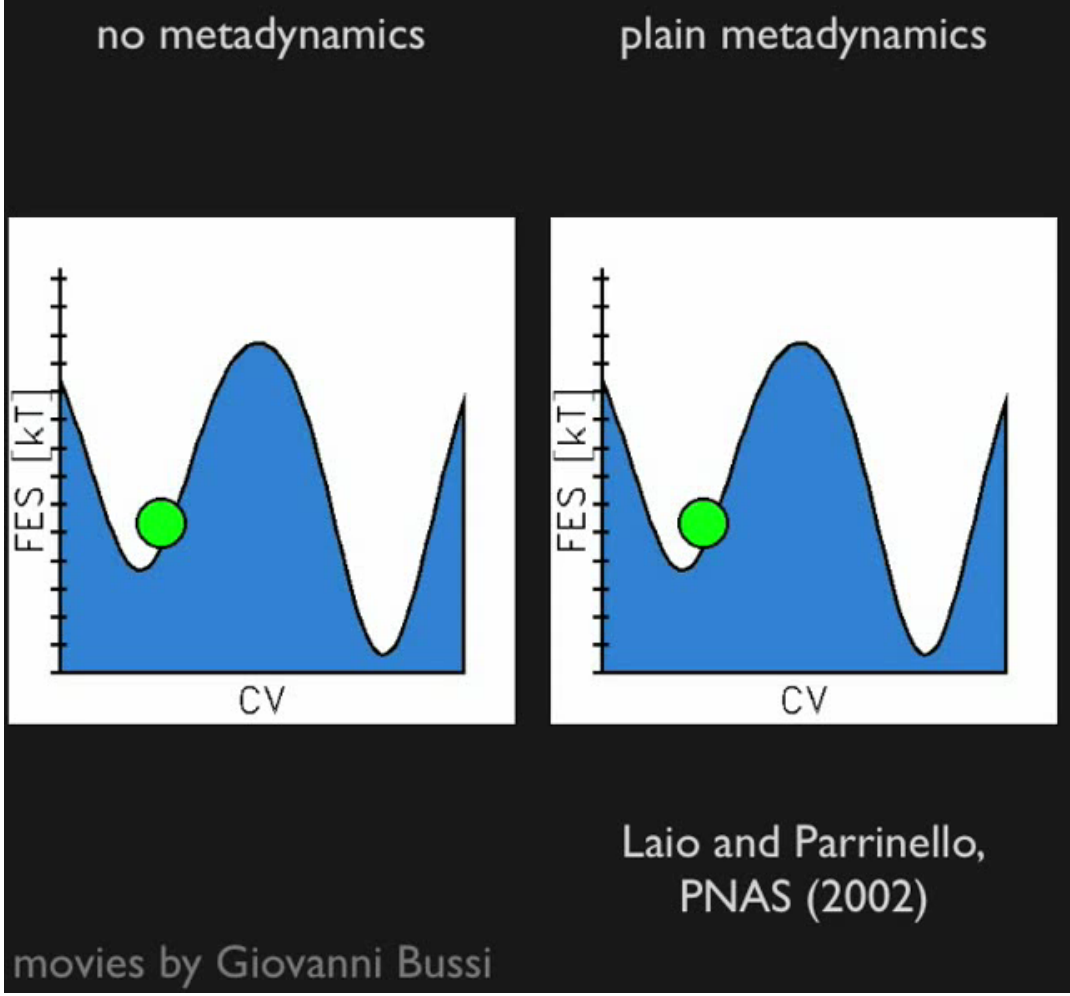
Ruin Cao et al., ***PlosONE*** 2015

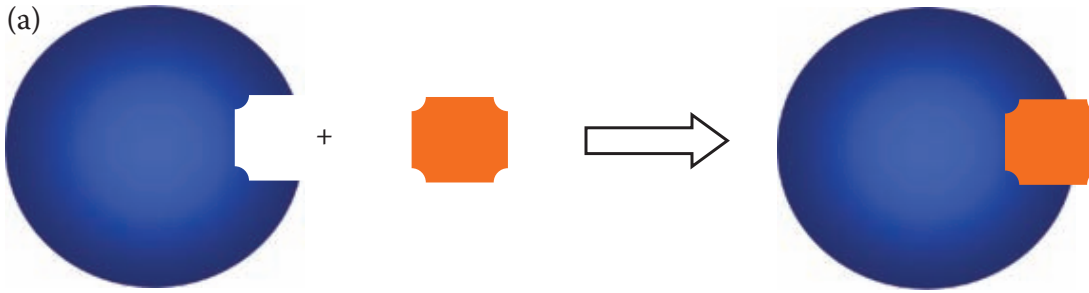
Enhanced sampling for ligand poses and affinities

A couple of Metadynamics Reviews from our group

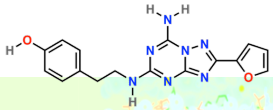
Leone et al. M. *Curr. Opin. Struct. Biol.*, **2010**

Biarnés et al. . *J. Comp.-Aided Mol. Design*, **2011**,

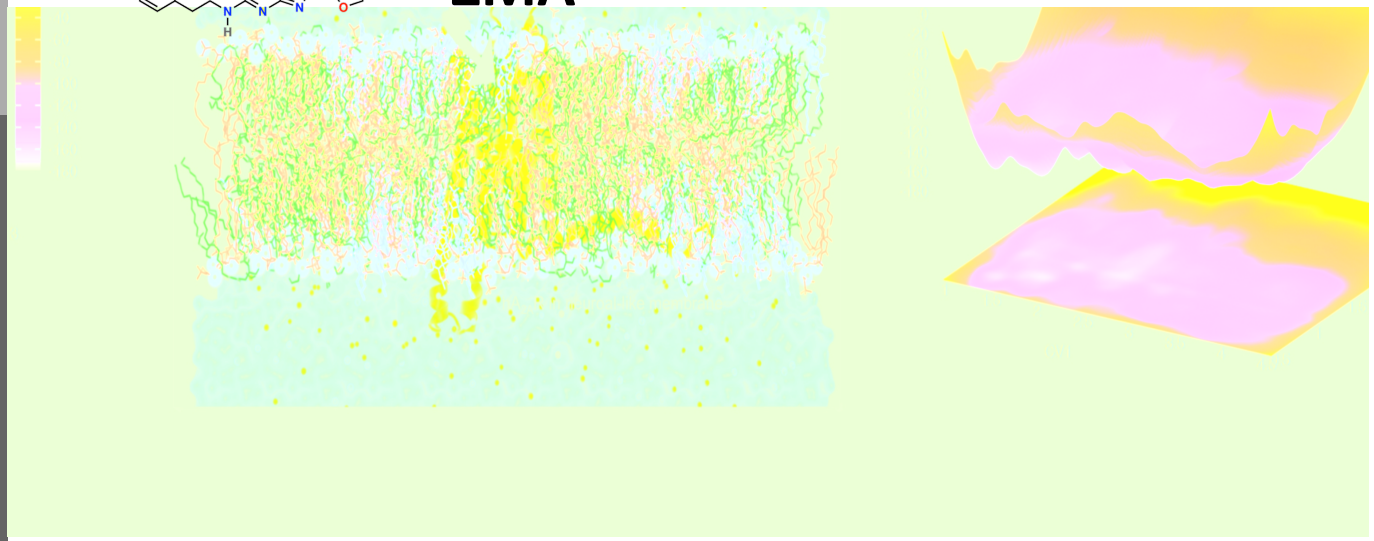


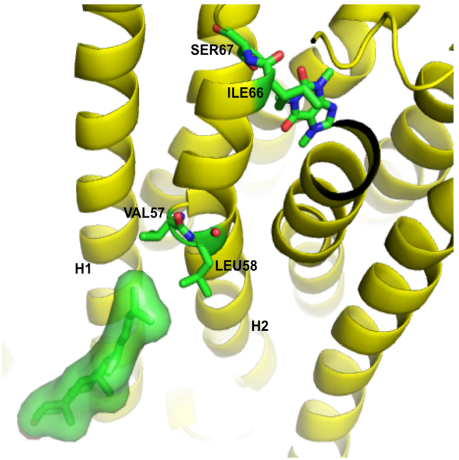


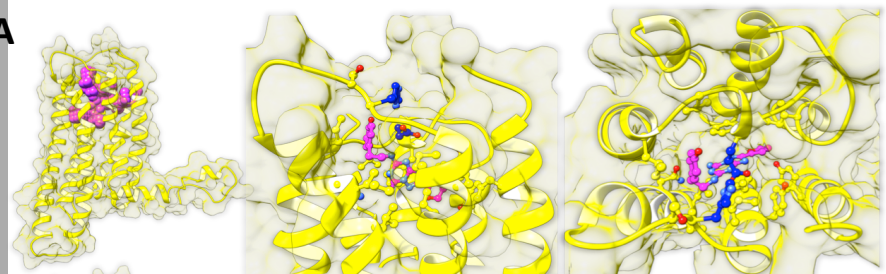
Ligand poses and affinities of a high affinity ligand of $hA_{2A}R$



ZMA





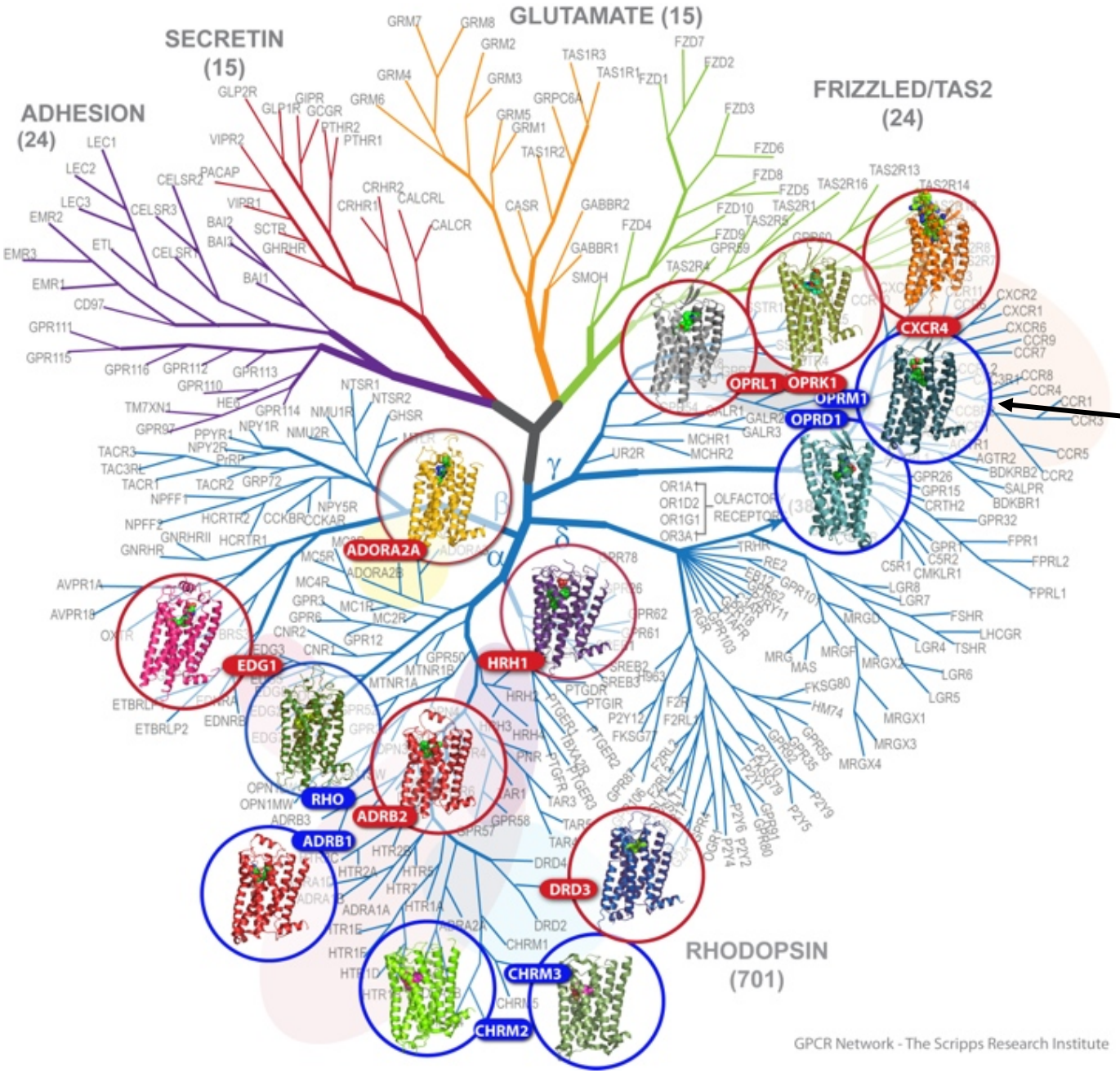


ΔG^0 (exp)=−13.2 kcal/mol
Guo et al. *Mol. Pharm.* 2016

ΔG^0 (calc) ≈−13.9 (8) kcal/mol

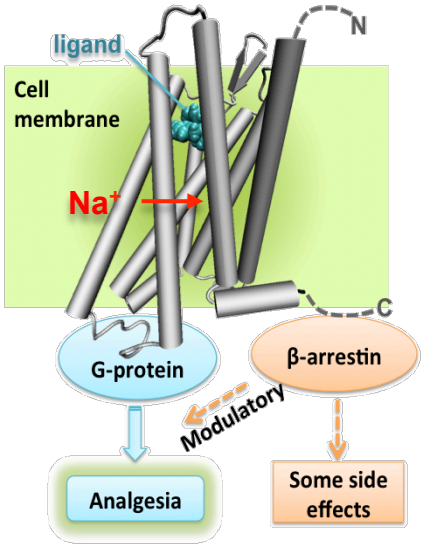
Cao et al, *PlosONE* 2015, submitted

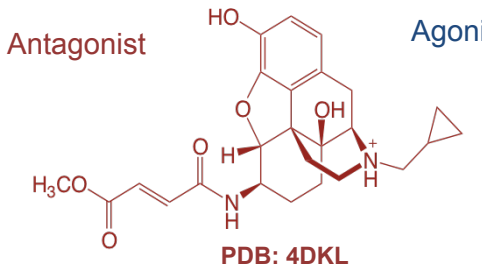
GPCR structural biology

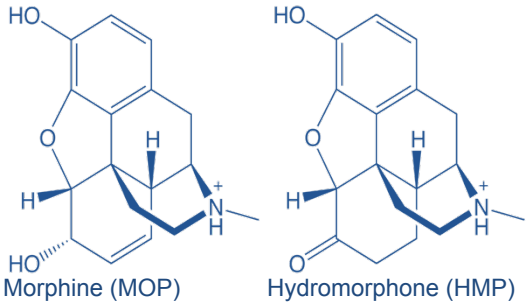


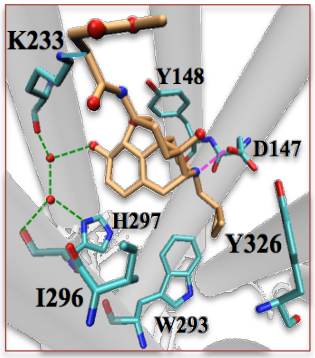
μ-Opioid receptor

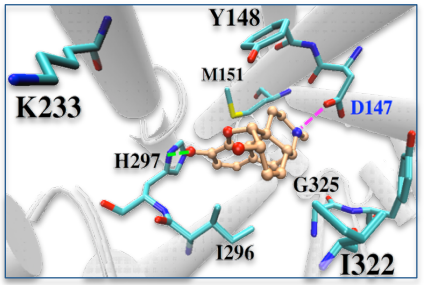
Painkillers targeting the μ-opioid receptor

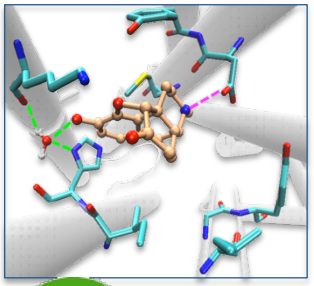


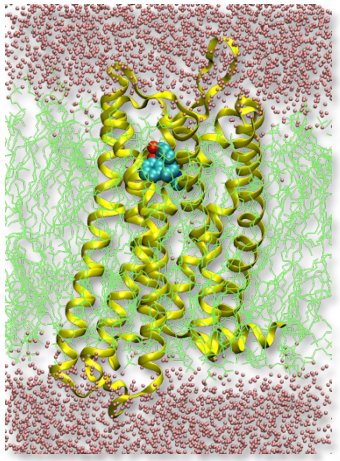








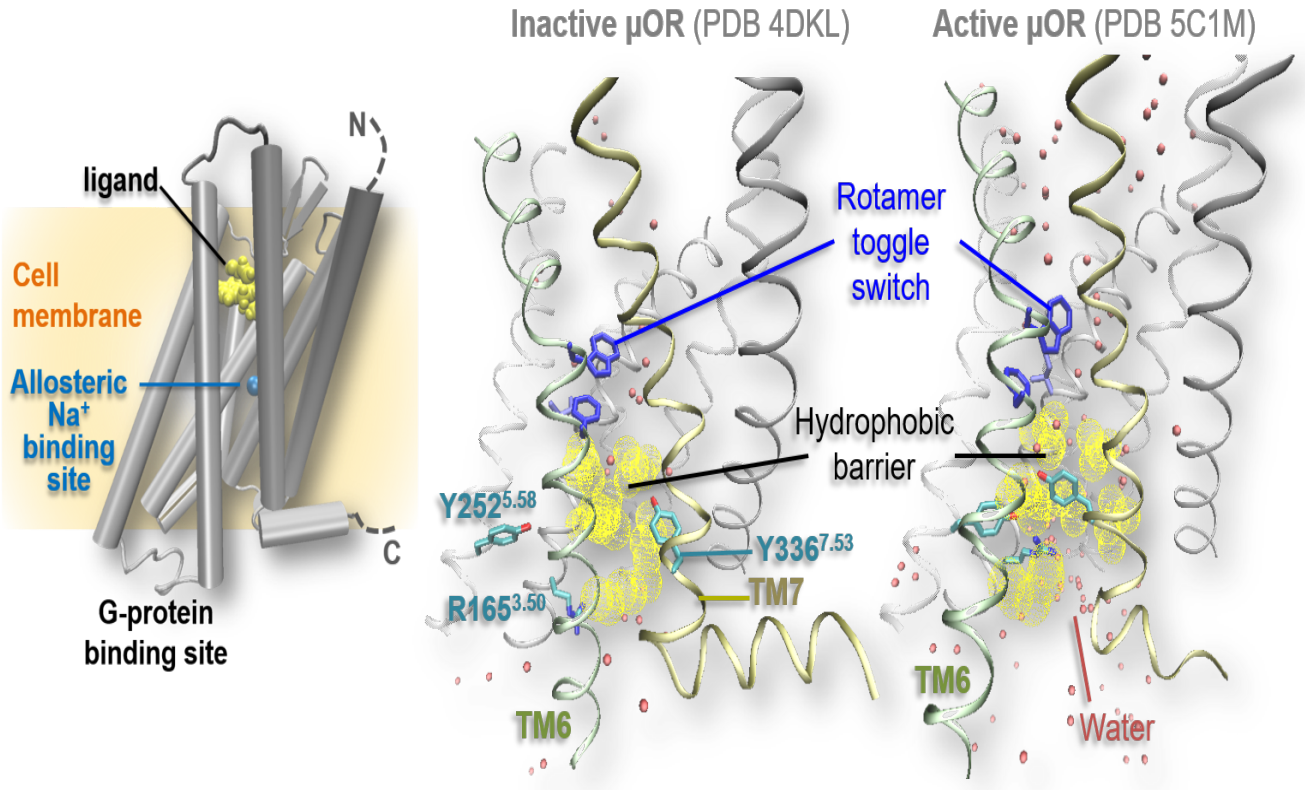




Binding free energy calculation (Alchemical transformation)
MOP→ HMP: 1.2±1.1 kcal/mol
HMP→ MOP: 0.8±0.8 kcal/mol Exp. 0.4±0.3 kcal/mol

Cong et al, *PlosONE* 2015

Activation



force fields:

- AMBER99SB-ILDN - **protein**
- Slipids – **membrane**
- TIP3P - **water** molecules

- PME for electrostatics
- NPT ensemble

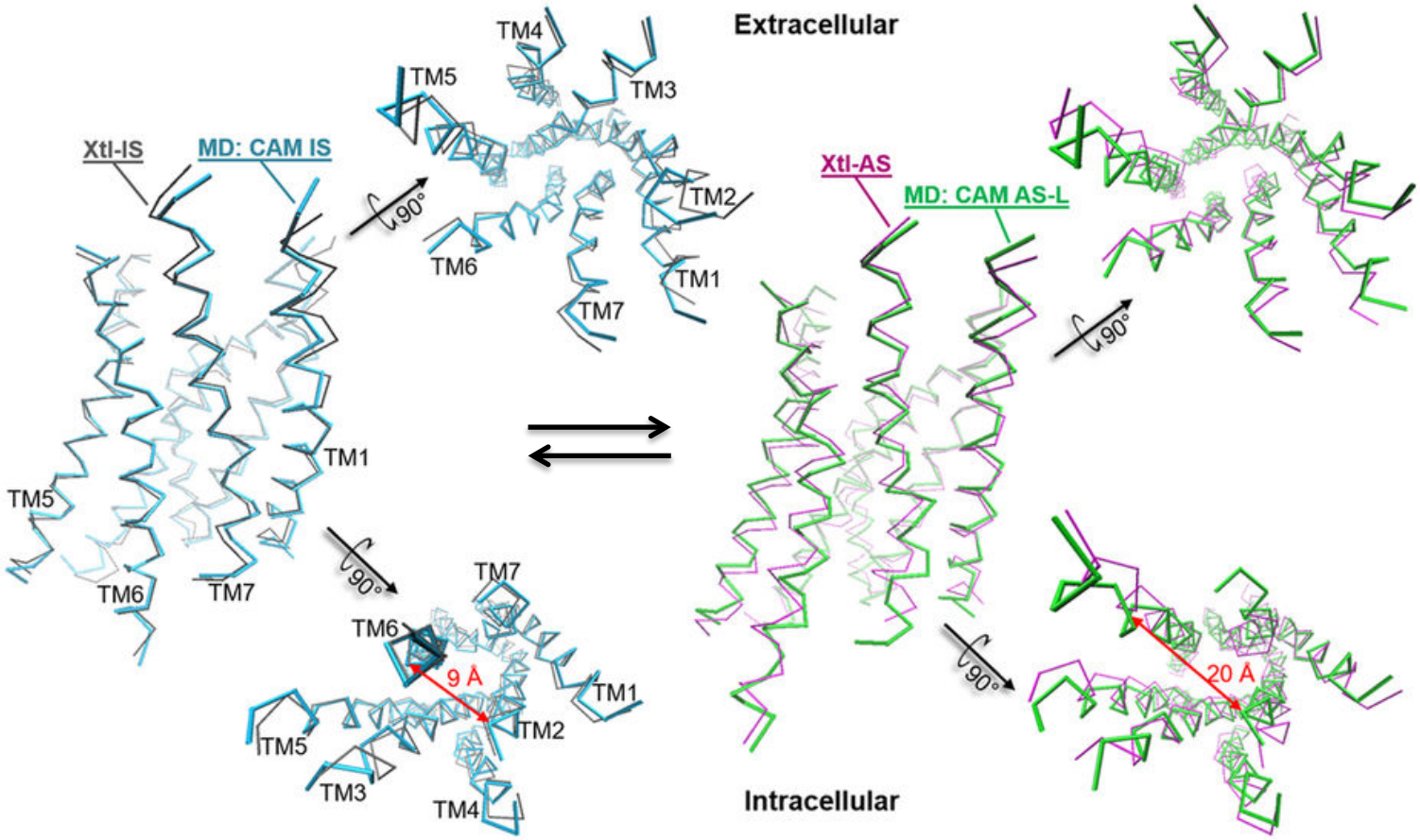
- REST2 : 20 ns × 64 replicas of MD simulations

- Wang, L., Friesner, R. A. & Berne, B. J. Replica Exchange with Solute Scaling: A More Efficient Version of Replica Exchange with Solute Tempering (REST2). *The Journal of Physical Chemistry B* **115**, 9431-9438.

-biology: *apo* μOR N150$^{3.35}$A CAM

-enhanced sampling: REST2

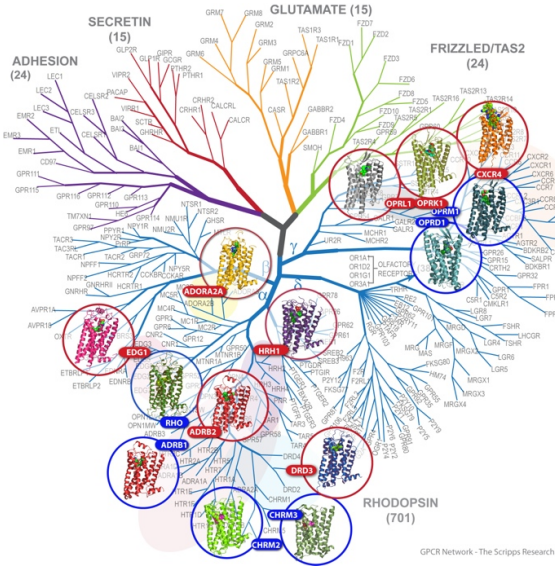
Interconversion IS (95%)- AS (5%) via few intermediates (not shown)



IS **AS**

Cong et al, Sci. Rep., 2017

1st/3rd Largest GPCR's families: Bitter and odorant receptors



Brain, respiratory system, gastrointestinal tract, endocrine system…

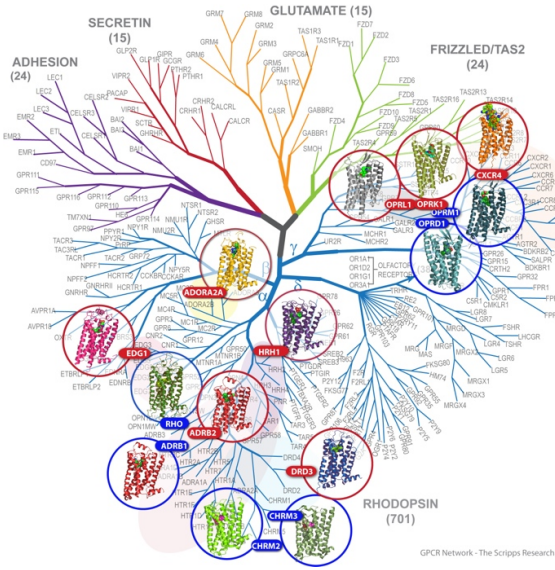
genetic variability on taste/odorant perception

novel therapies

Soranzo et al *Curr Biol* 2005; Wu et al. *PNAS* 2002

Singh et al, *BBRC* 2011; Lee et al. *J Mol Med* 2014

Largest GPCR's families:
Bitter and odorant receptors

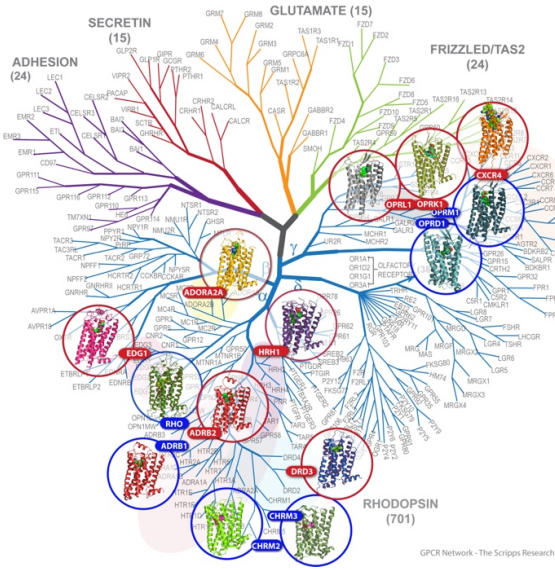


TAS2R family
25 members in humans
recognizing hundreds of food compounds

Others (TAS2R38): few agonists binding
Some (TAS2R46): large agonist diversity
access control "for wrong bitter compounds?"

Meyerhof et al. PNAS 2010

Largest GPCR's families: Bitter and odorant receptors



TAS2R family
25 members in humans
recognizing hundreds of food compounds

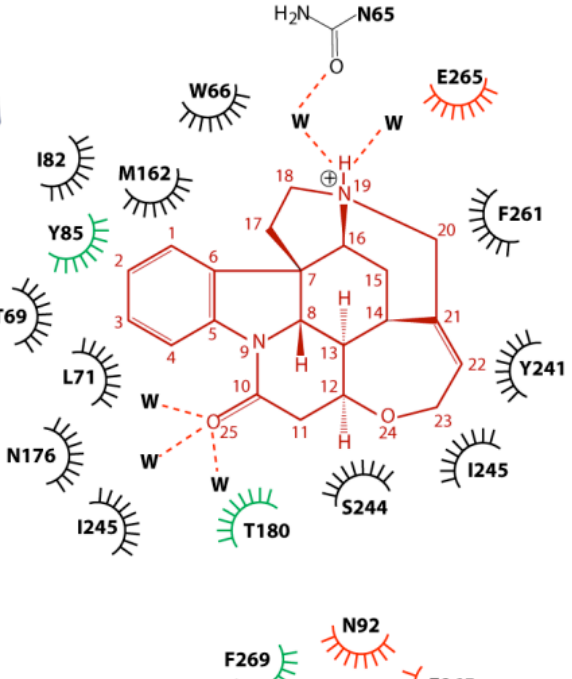
Predicting binding poses?

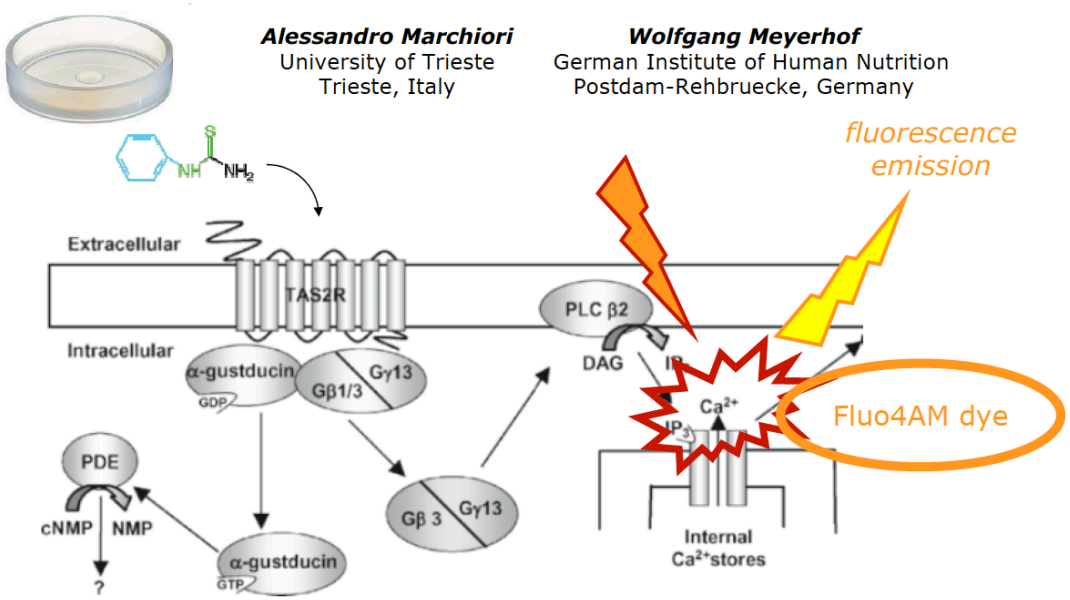
1. **No structural information**
2. **SI with templates <20%**
3. **Only molecular biology experiments (Meyerhof's group)**

Essays on wild-type and mutant bitter taste receptors

TP= # true positives , FP=# false positives
FN= false negatives

PREC = TP / (TP+FP)
REC = TP / (TP+FN)

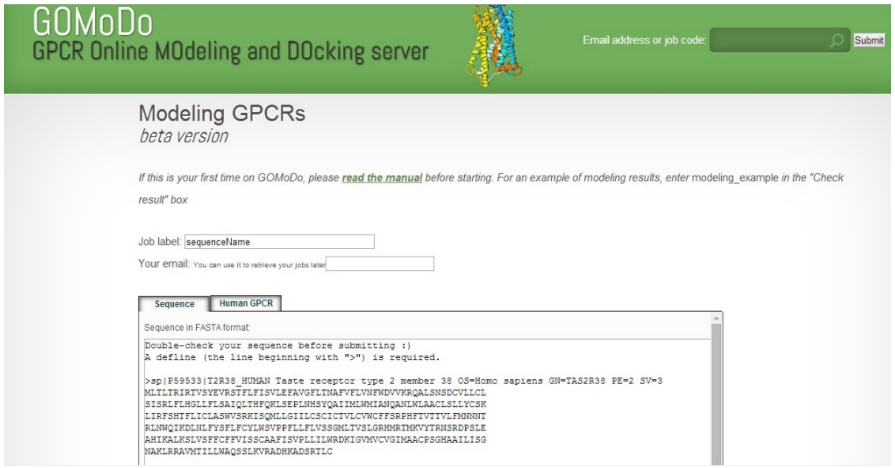


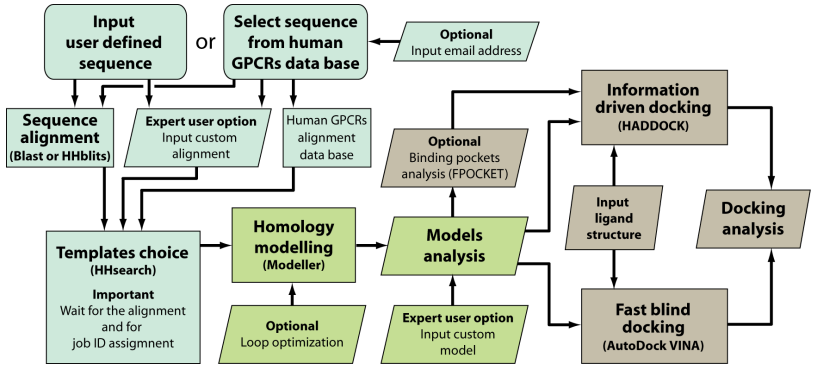


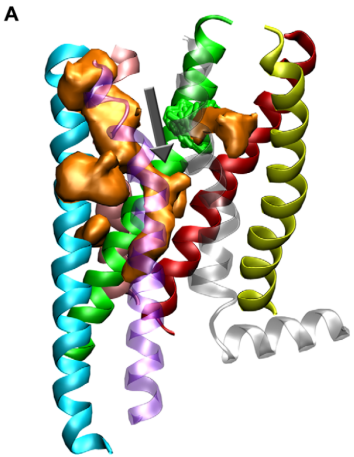
Step #1: Bioinformatics + docking

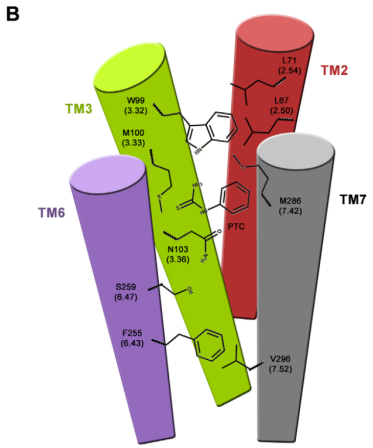
1. Available Structural Data
2. Evolutionary Information
3. Sequence based structural/ functional assessment

Structural Modeling of ligand/GPCR complexes





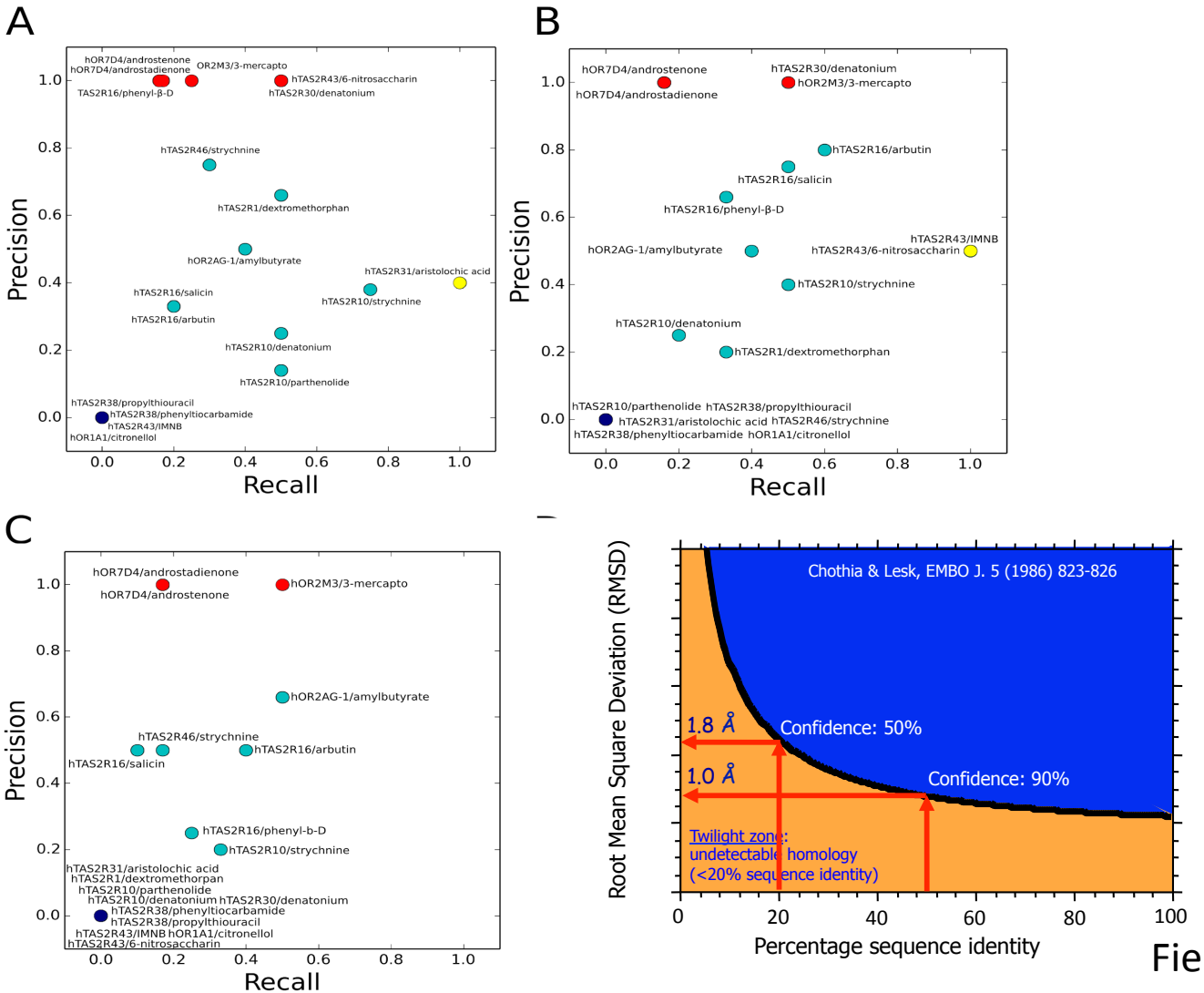




Alejandro Giorgetti

Kamil Khafizof

Step #1: Bioinformatics + docking



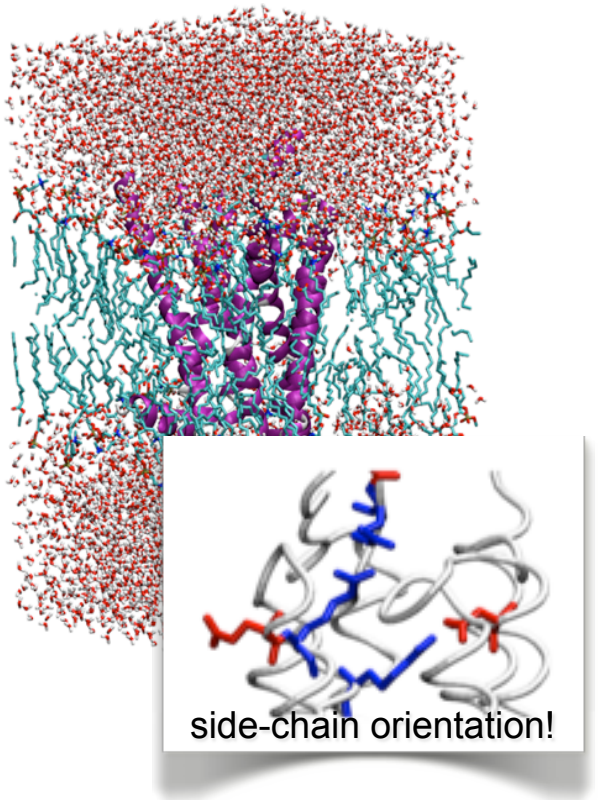
Fierro et al, submitted.

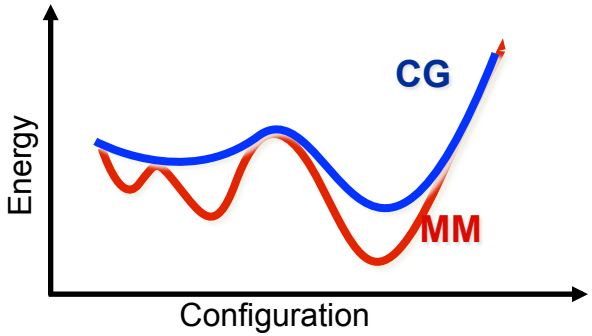
Step #2: Molecular Simulation

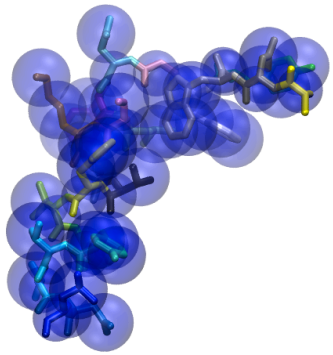
JÜLICH FORSCHUNGSZENTRUM

all-atom model

coarse grain model







MM: all-atom

CG: coarse-grained

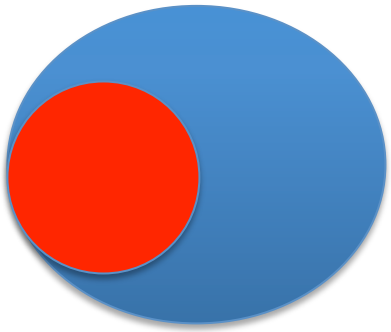
Ligand binding

Hybrid methods

JÜLICH FORSCHUNGSZENTRUM

Investigating structure, dynamics and energetics of proteins by molecular dynamics at at different levels of granularity (quantum-mechanical, all-atoms force field, coarse grain)

→Combining different descriptions



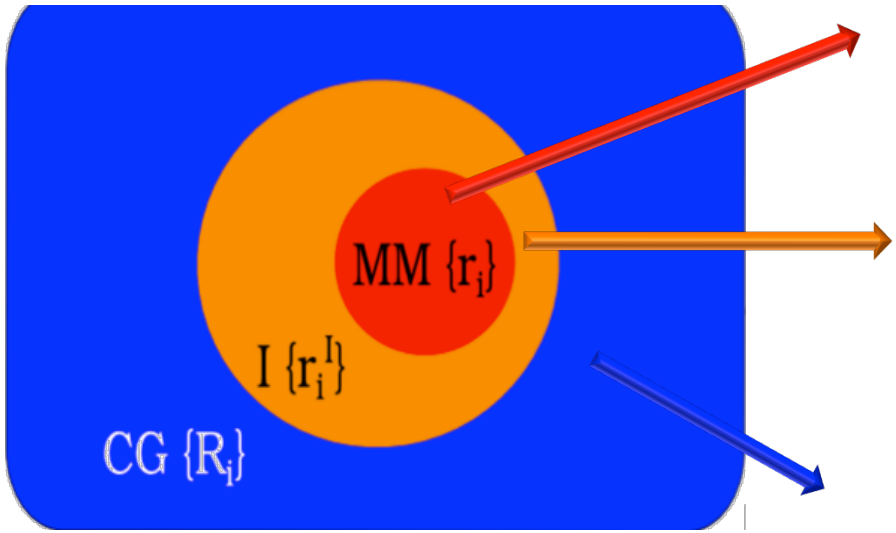
Coarse-grain/classical mechanics

Hybrid Coarse-Grain/Molecular Mechanics simulations

PRL 95, 218102 (2005) PHYSICAL REVIEW LETTERS week ending 18 NOVEMBER 2005

Coarse-Grained Model of Proteins Incorporating Atomistic Detail of the Active Site

Marilisa Neri,[1] Claudio Anselmi,[1] Michele Cascella,[2] Amos Maritan,[3] and Paolo Carloni[1,*]
[1]*SISSA/ISAS and INFM-DEMOCRITOS Modeling Center, Via Beirut 4, I-34014 Trieste, Italy*
[2]*Ecole Polytechnique Fédérale de Lausanne (EPFL), CH-1015 Lausanne, Switzerland*
[3]*Dipartimento di Fisica and INFN, Università degli Studi di Padova, Via Marzolo 8, I-35131 Padova, Italy*
(Received 20 April 2005; published 16 November 2005)



MM: Region of interest
(e.g. protein active site)
Atomistic force field (Gromos, Amber)

Interface region
Atomistic force field coupled to CG

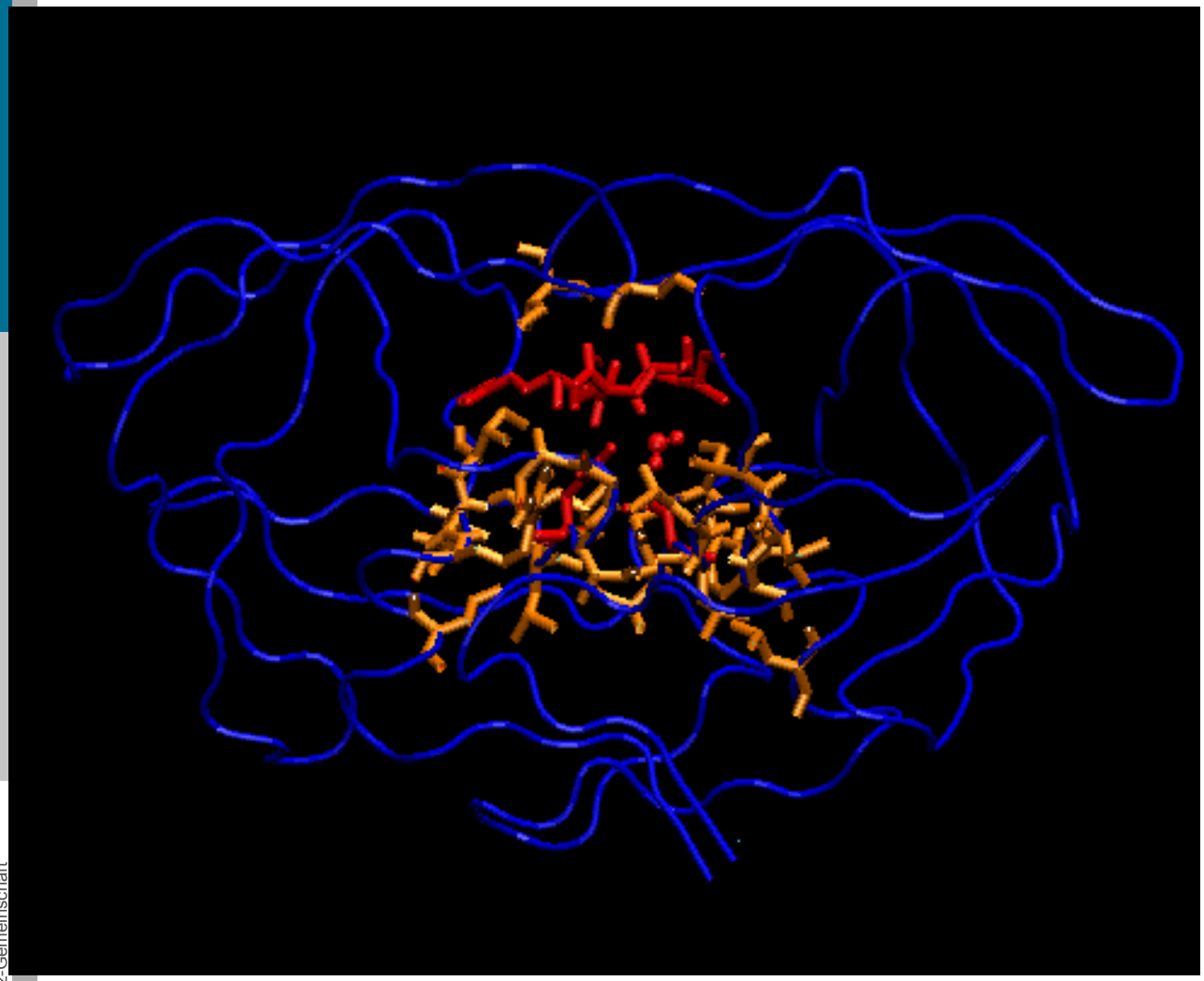
CG: Protein frame
Go-model
(e.g. Cα backbone atoms only)

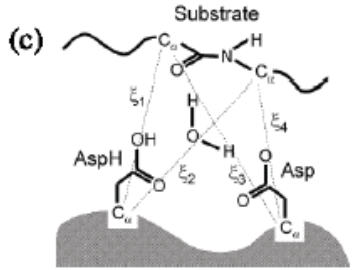
$$V = E_{MM} + E_I + E_{I/MM} + E_{CG} + E_{CG/I}$$

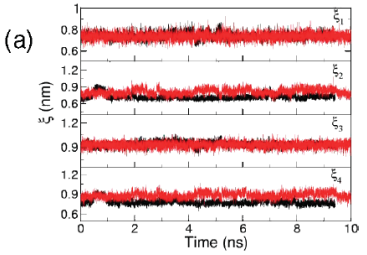
$$E_{\mathrm{MM}} = E_{\mathrm{bond}} + E_{\mathrm{vdW}} + \sum_{i>j} \frac{q_i q_j}{\varepsilon |\mathbf{r}_i - \mathbf{r}_j|},$$

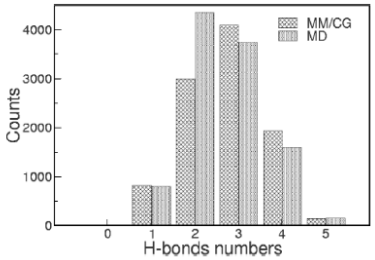
$$E_{CG} = \frac{1}{4}\sum_i K_b(|R_i - R_{i+1}|^2 - b_{ii+1}^2)^2 + \sum_{i>j} V_0\{1 - \exp[-B_{ij}(|R_i - R_j| - b_{ij})]\}^2$$

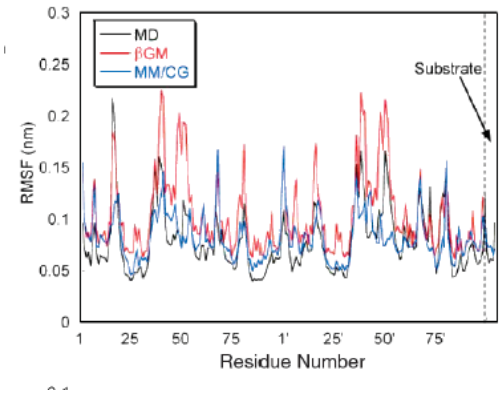
Test #1: A cytoplasmatic protein



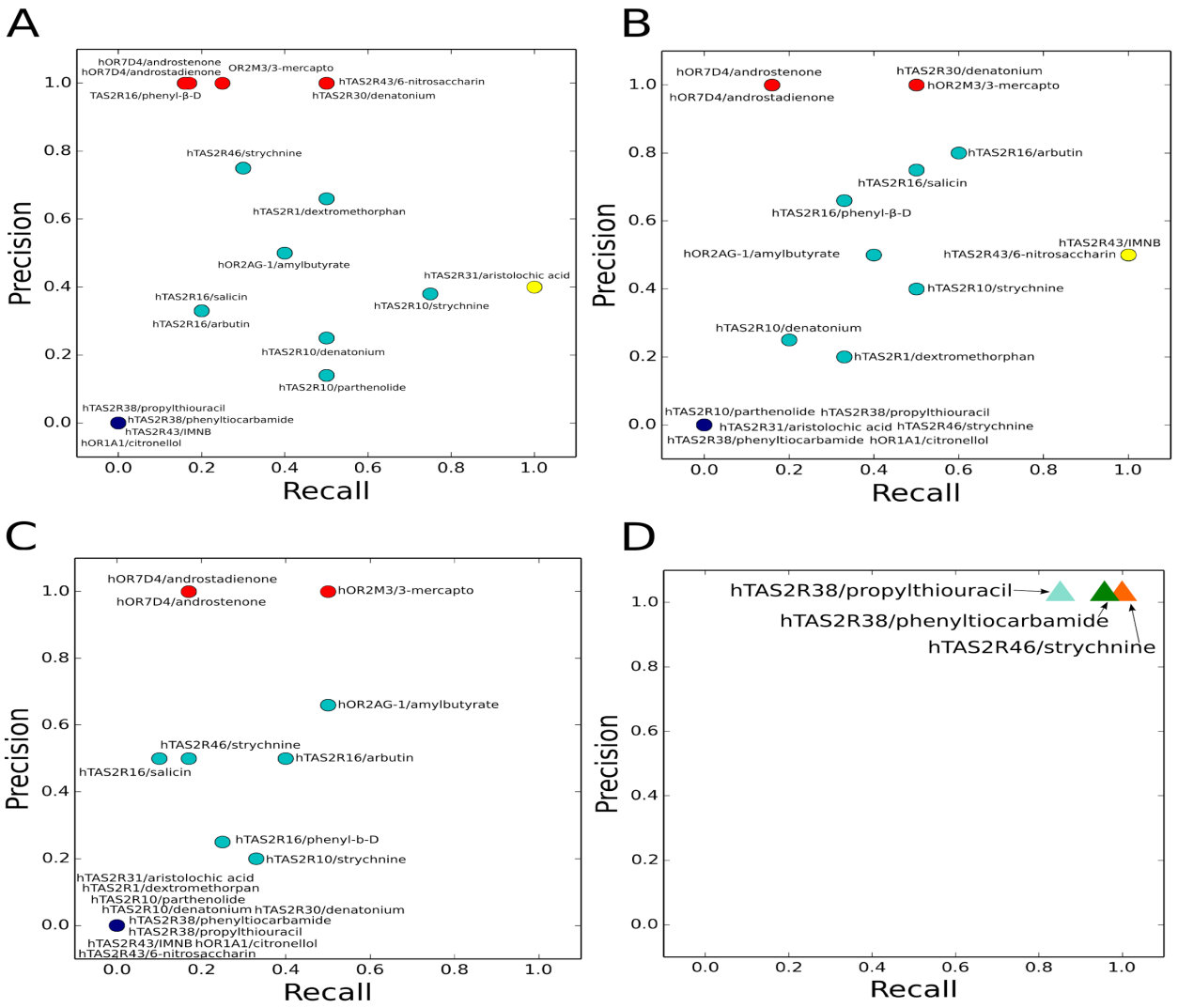






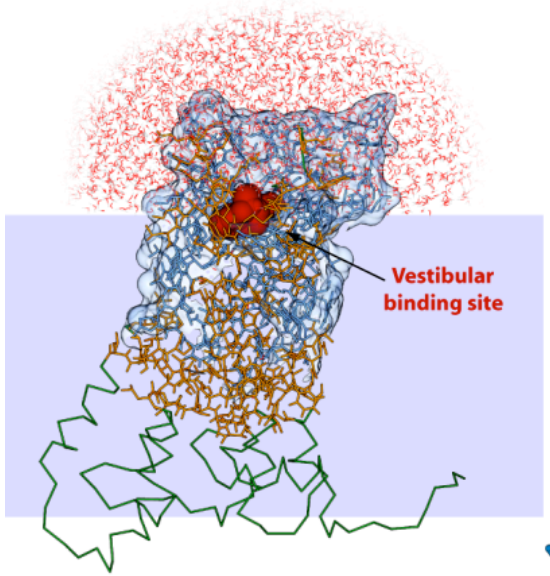


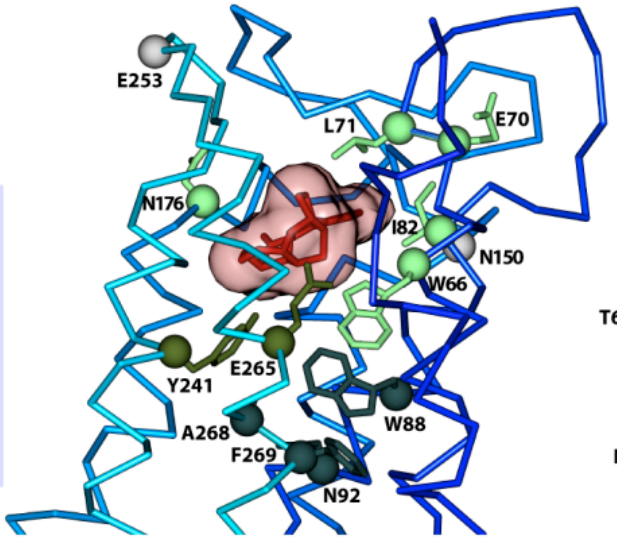
Coarse grain/MD of TAS2R46 And TASR38 in complex with agonists

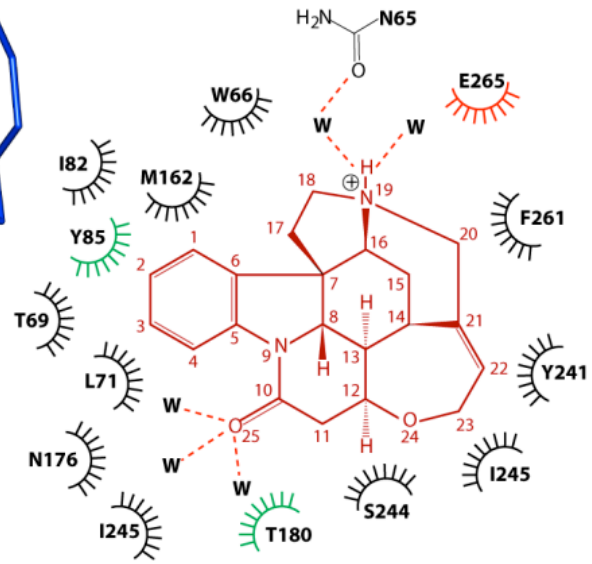


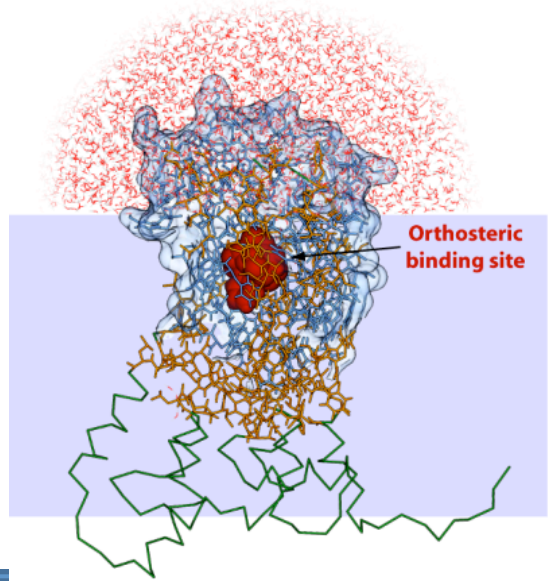
Coarse grain/MD of TAS2R46/ Strychnine (Large ligand diversity)

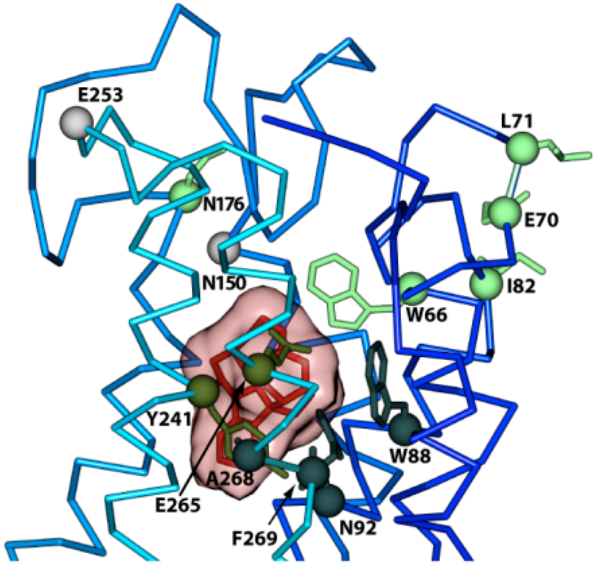
JÜLICH FORSCHUNGSZENTRUM

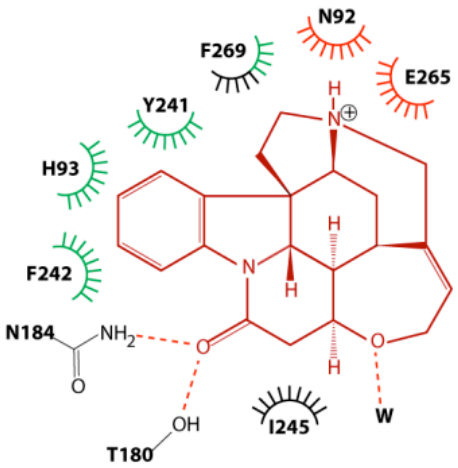






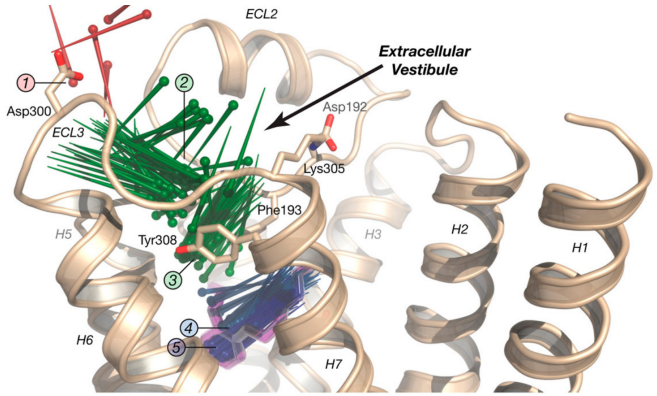




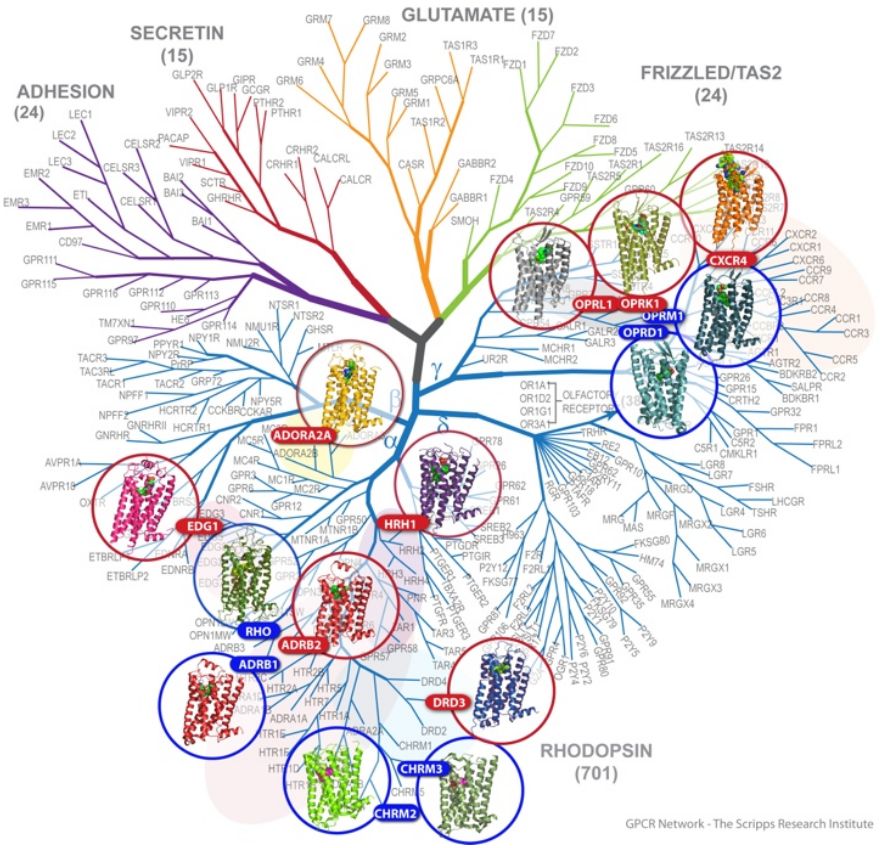


‘Vestibular' binding site across GPCRs

Muscarinic, β2-adrenergic , opioid receptors: two cavities



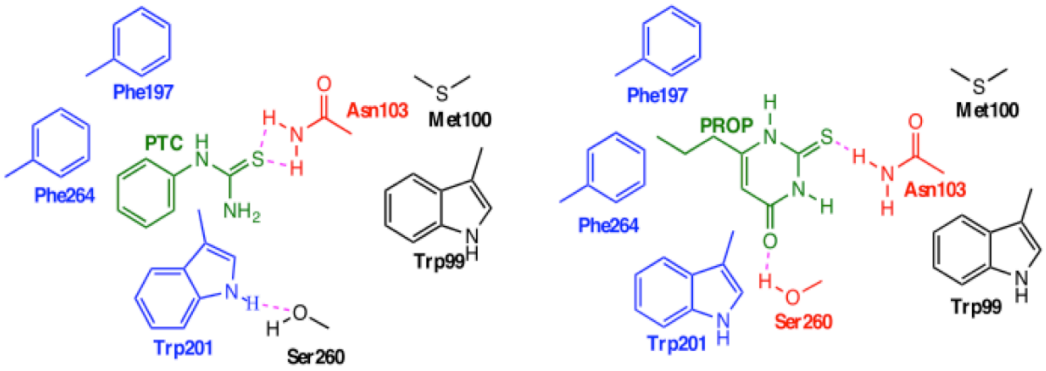
alprenolol/β2-adrenergic



Dror et al. *PNAS* 2011, *Nature* 2013
Granier. & Kobilka, *Nat. Chem. Biol*. 2012

TAS2R8: Only one binding site

- Predictions consistent with more than 20 site-directed mutagenesis and functional calcium imaging experiments



Marchiori et al. *PLOS ONE* 2013

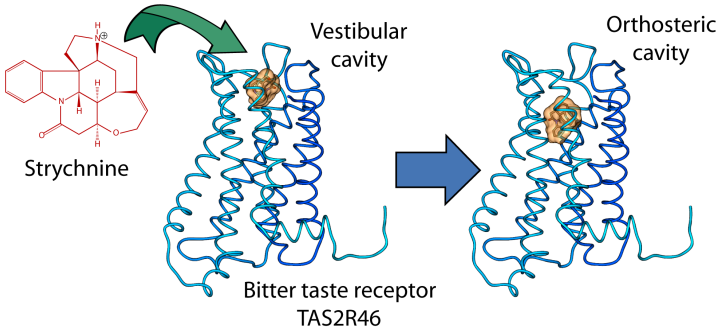
Variant	Agonist PTC EC_{50} (uM)	PTC Max act	PROP EC_{50} (uM)	PROP Max act
WT	2.5 (**3**)	0.43 (**0.47**)	2.17	0.44
Trp99 Ala	1.2 (**4.25**)	0.14 (**0.25**)	1.8	0.59
Trp99 Val	1.8 (**2.7**)	0.28 (**1.12**)	5~	0.93
Met100 Ala	4.1 (**3**)	0.72 (**1.01**)	1.2	0.77
Met100 Val	21.2* (**10**)	0.51 (**0.79**)	1.8	0.42
Asn103 Ala	6.6* (**8**)	0.21 (**0.38**)	8.7*	0.65
Asn103 Val	6.9* (**15**)	0.09 (**0.09**)	9.1*	0.41
Asn103 Asp	-	0.06	23.8*	0.13
Asn179 Ala	4.4	0.34	4.9	0.32
Asn179 Val	4.9	0.29	5	0.30
Arg181 Ala	2.2	0.26	4.3	0.26
Arg181 Val	4.5	0.17	7.5	0.19
Asn183 Ala	4.2	0.36	5.3	0.32
Asn183 Val	2.5	0.44	3.1	0.40
Phe197 Val	4.3	0.06	9.9*	0.12
Trp201 Leu	-	0.25	-	0.02
Trp201 Phe	21*	0.14	-	0.05
Ser259 Ala	5.7 (**5.4**)	0.55 (**0.42**)	2.9	0.45
Ser259 Val	99* (**27**)	0.02 (**0.04**)	21.8*	0.18
Ser260 Ala	1.41	0.21	1.14	0.45
Ser260 Val	9.8*	0.03	6.8*	0.09
Phe264 Ala	-	0,06	-	0,06
Phe264 Val	12.4*	0.06	25.9*	0.24

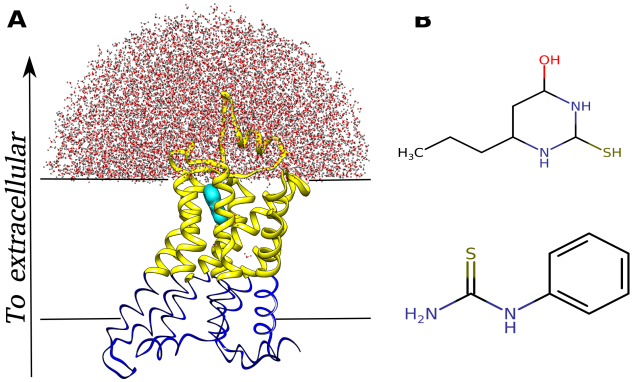
Modulating selectivity: from 2-state to 1-state binding

JÜLICH FORSCHUNGSZENTRUM

Input: sequence/ chemical structure compound

Agonist structural diversity





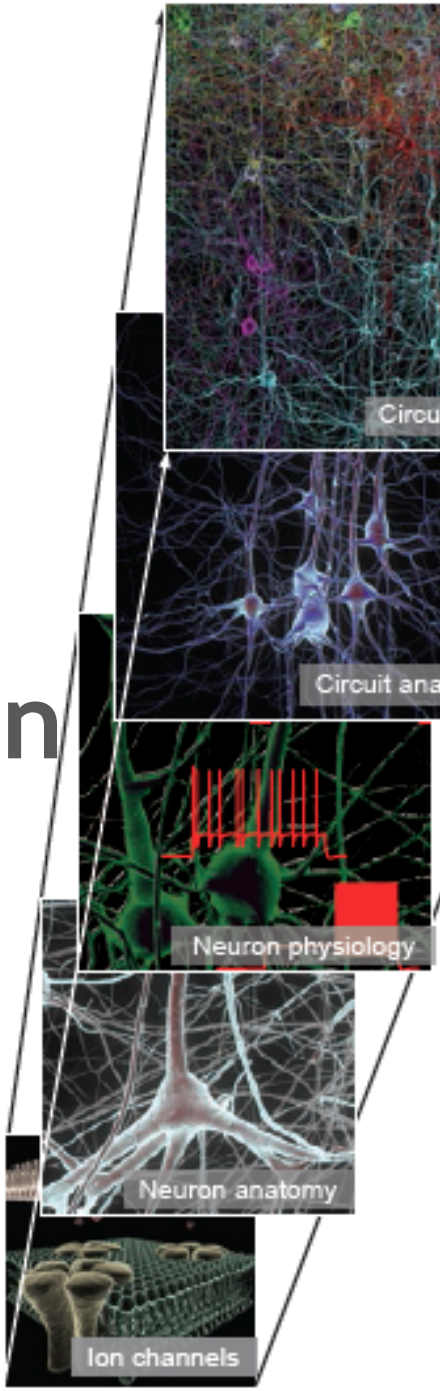
Sandal et al,
J. Chem. Theory Comp. 2015

FET FLAGSHIPS

Human Brain Project

European Commission

Multi-scale molecular simulation in the human brain project

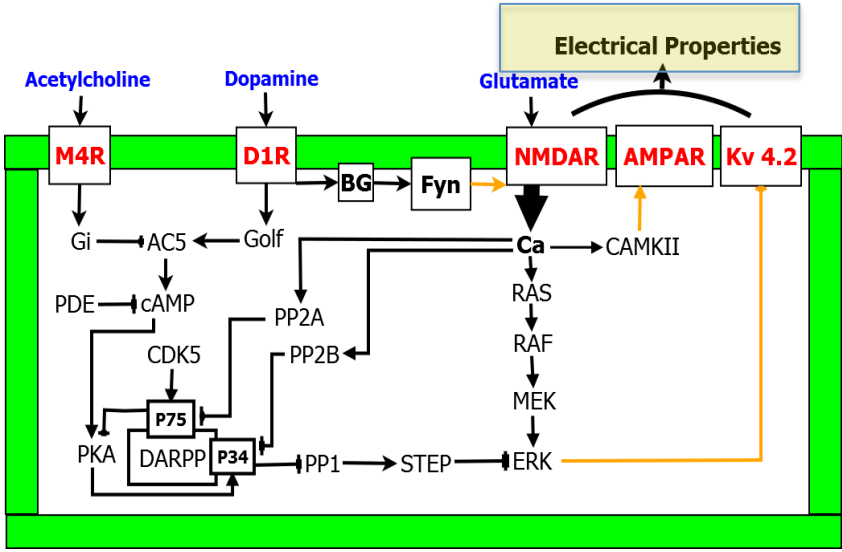


SP6

GPCRs-based signaling pathway involved in memory processes

- **Case study:** Receptor induced cascades leading to activation of kinases and phosphatases, integrated into a neuron model

  Proof of concept: https:/collab.humanbrainproject.eu/#/collab/489/nav/5364).



Nair, et al (2015) J Neuroscience

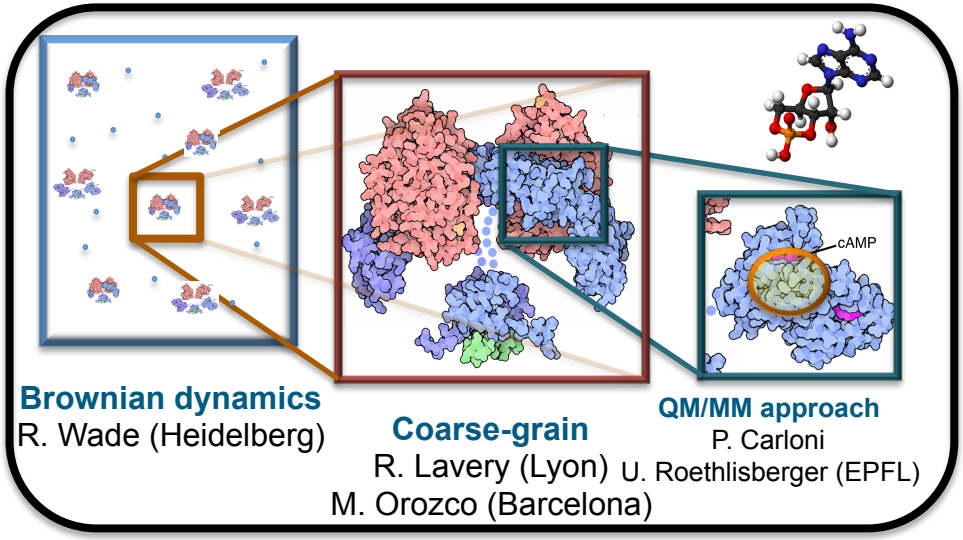
- **Molecular Dynamics**

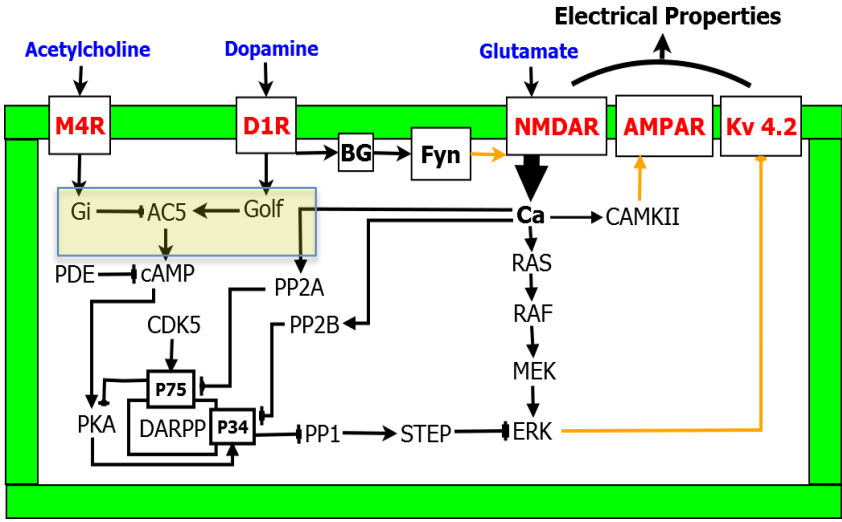
-Input data for systems biology (at times not accessible from experiment)

-Molecular details of neuronal cascades relevant for higher level models

SP6

Multi-scale molecular simulation and systems biology





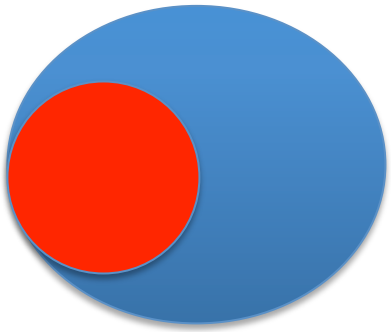
General approach for
-kinetic parameters
-molecular insights

Hybrid methods

JÜLICH FORSCHUNGSZENTRUM

Investigating structure, dynamics and energetics of proteins by molecular dynamics at at different levels of granularity (quantum-mechanical, all-atoms force field, coarse grain)

→Combining different descriptions



Quantum mechanics/classical mechanics

QM/MM simulations

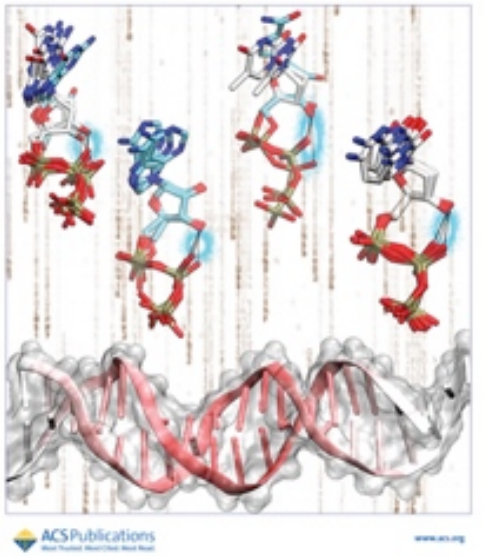
CPMD code
DFT
BLYP, BP, B3LYP XC functionals
Basis set: PW (90 Ry)
Martins Troullier pseudopotentials
Thermodynamic integration, metadynamics

Amber Force Field, Gromos96 Code

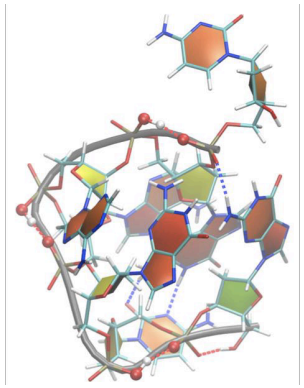
Laio et al, ***JCP*** 2002
Dal Peraro et al. ***Curr Op. Str. Biol.*** 2007

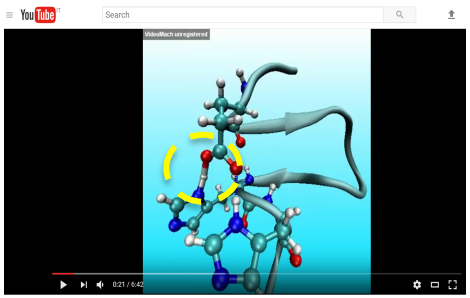
DNA pol enzymatic reaction
Genna et al., 2016

Spotlights of JACS publications
2016, 138, 14507



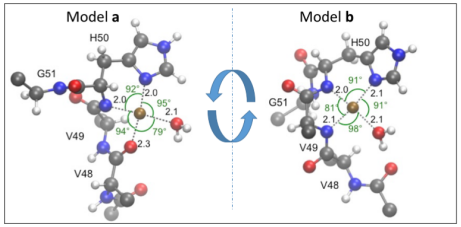
Mass spectrometry
(with Modesto Orozco)





Arcella et al, Angew. Chem. 2015
Li et al, J. Phys Chem Lett 2017

Copper(II) binding sites

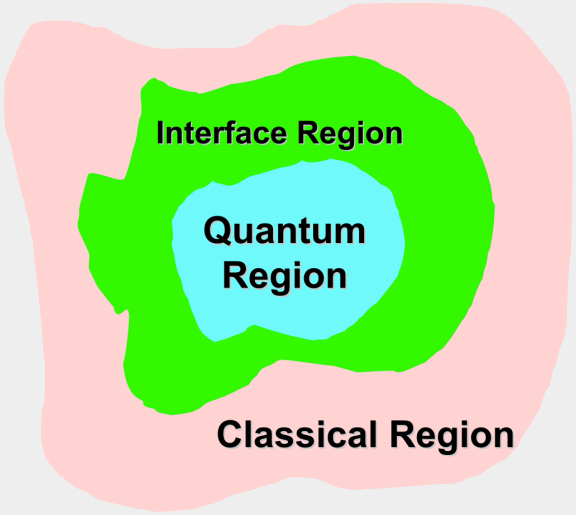


Villar-Pique et al., *PNAS,* 2016

Hybrid QM/MM molecular dynamics

$$L_{\mathrm{CPMD}} = L_{\mathrm{MD}} + \frac{1}{2}\sum_i \mu_i \int \mathrm{d}\mathbf{r}\, |\dot{\psi}_i|^2 - V_{\mathrm{DFT}}(\mathbf{R},\mathbf{r}) + \sum_i \sum_i \Lambda_{ij}\left(\int \psi_i^* \psi_j \,\mathrm{d}\mathbf{r} - \delta_{ij}\right)$$

$$\rho(\mathbf{r}) = \sum_i |\psi_i(\mathbf{r})|^2$$



$$V_{\mathrm{DFT}}(\mathbf{R},\mathbf{r}) = \sum_I \sum_{J>I} \frac{q_I q_J}{R_{IJ}} - \frac{1}{2}\sum_i \int \mathrm{d}\mathbf{r}\, \psi_i^*(\mathbf{r})\nabla^2\psi_i(\mathbf{r}) + \int \mathrm{d}\mathbf{r}\, V_{\mathrm{N}}(\mathbf{R})\rho(\mathbf{r}) + \frac{1}{2}\int \mathrm{d}\mathbf{r}\,\mathrm{d}\mathbf{r}' \frac{\rho(\mathbf{r})\rho(\mathbf{r}')}{|r_{ij}|} + E_{\mathrm{XC}}[\rho(\mathbf{r})]$$

$$L_{\mathrm{QM/MM}} = L_{\mathrm{CPMD}} + L_{\mathrm{MM}} - \sum_{i\in\mathrm{MM}} q_i \int \mathrm{d}\mathbf{R}\, \rho(\mathbf{r}) V_i(|\mathbf{R} - \mathbf{R}_i|)$$

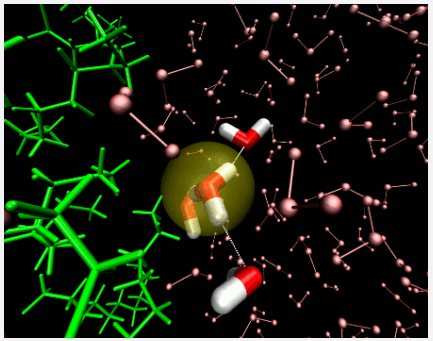
Laio et al., JCP, 2002

QM/MM Simulations

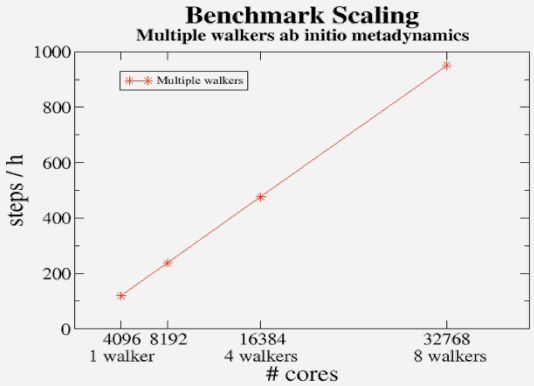
Problems:

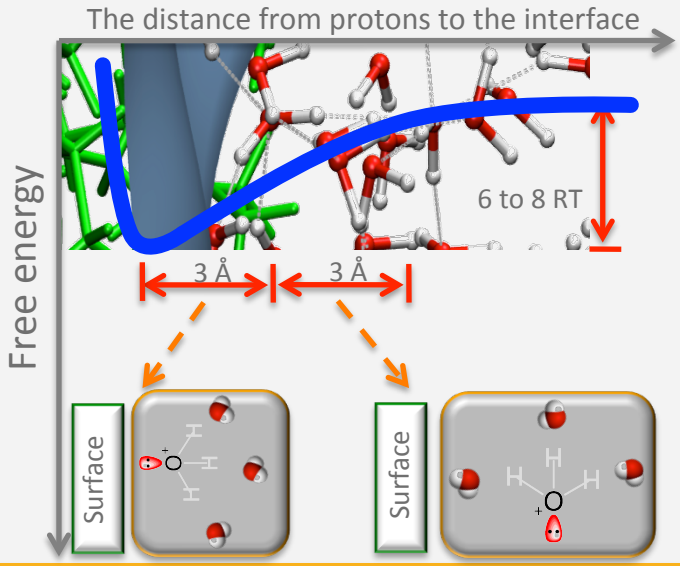
- Poor scalability –sampling issues

CPMD calculation: Energetics of proton translocation



Zhang et al., *PNAS,* 2012





QM/MM Simulations

Problems:

- Poor scalability –sampling issues
- Limited number of available force-fields
- Proprietary GROMOS96 license

New HPC-based Approach

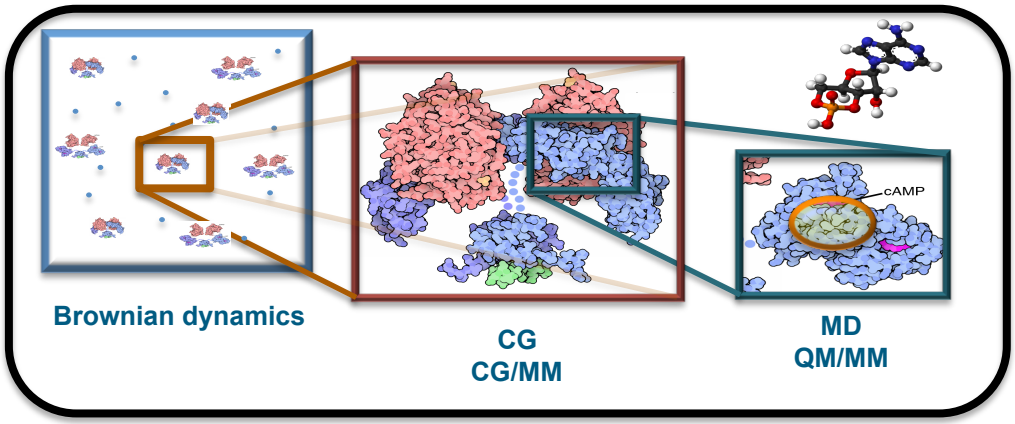
- ✓ Design the architecture of an interface
- ✓ Design the protocol for data movement
- ✓ Develop the communication library
- ✓ Develop the QM/MM interface
- ⚠ Coupling to GROMACS (http://www.gromacs.org/)
- ✓ Writing the contributor manual
- ✓ Going open-source
- ✓ Performance and scaling optimizations
- ✓ Adopting different model for electrostatics treatment

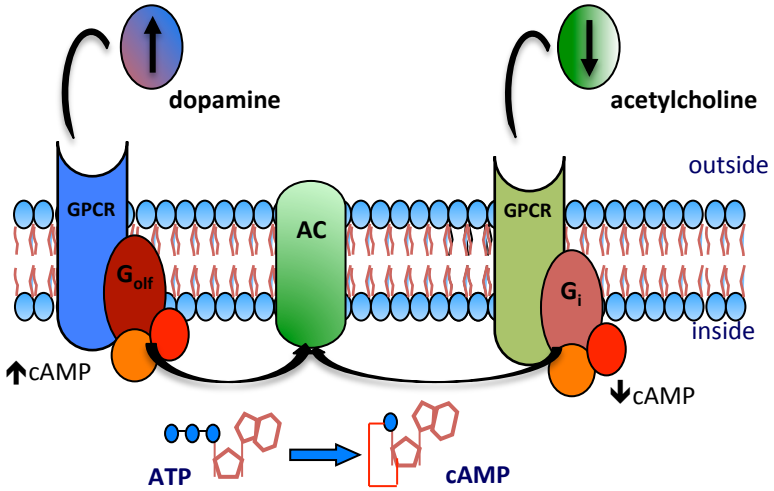
- Viacheslav Bolnykh
  RWTH-Aachen
- Emiliano Ippoliti
  FZJ, Juelich
- Dr. Jógvan Magnus Hausgaard Olsen
  University of Southern Denmark
- Dr. Simone Meloni
  University La Sapienza

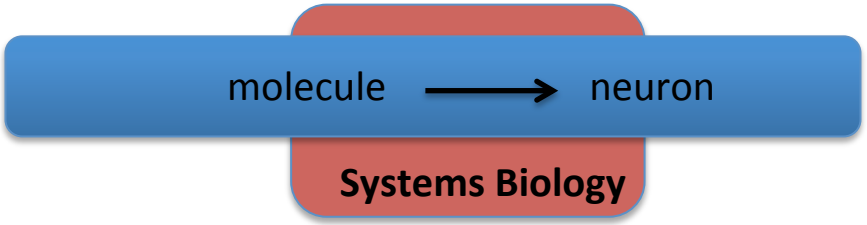
- **Prof. Ursula Röthlisberger**
  EPFL, Lausanne
- Dr. Teodoro Laino
  IBM, Zürich
- Dr. Valery Weber
  IBM, Zürich
- Dr. Alessandro Curioni
  IBM, Zürich
- Erik Lindahl
  KTH, Stockholm

HPC-LEAP
EUROPEAN JOINT DOCTORATES
bioexcel

Multiscale simulations of neuronal receptors







Acknowledgements

Vania Calandrini, Alejandro Giorgetti, Massimo Sandal, Xevi Biarnes, Michael Leguebe, Giulia Rossetti, Mercedes Alfonso Prieto, Luca Maggi, Xiaojing Cong, Fabrizio Fierro
Prof Meyerhof‘s group (German institute of Nutrition, Potsdam, Germany),
Prof. Katrin Amunts (FZJ, Germany)
Prof. Sven Cichon (FZJ)
Prof. Andreas Bauer‘s (FZJ)
Prof. B. Neumeier (FZJ)

Funding: DFG, BMBF, Ernesto Illy Foundation, Human Brain Project, JARA, BioExel, HPC Leap

, May 2017

Neurodegenerative diseases

JÜLICH FORSCHUNGSZENTRUM

Gradual and progressive loss of neural cells, leading to nervous system dysfunction

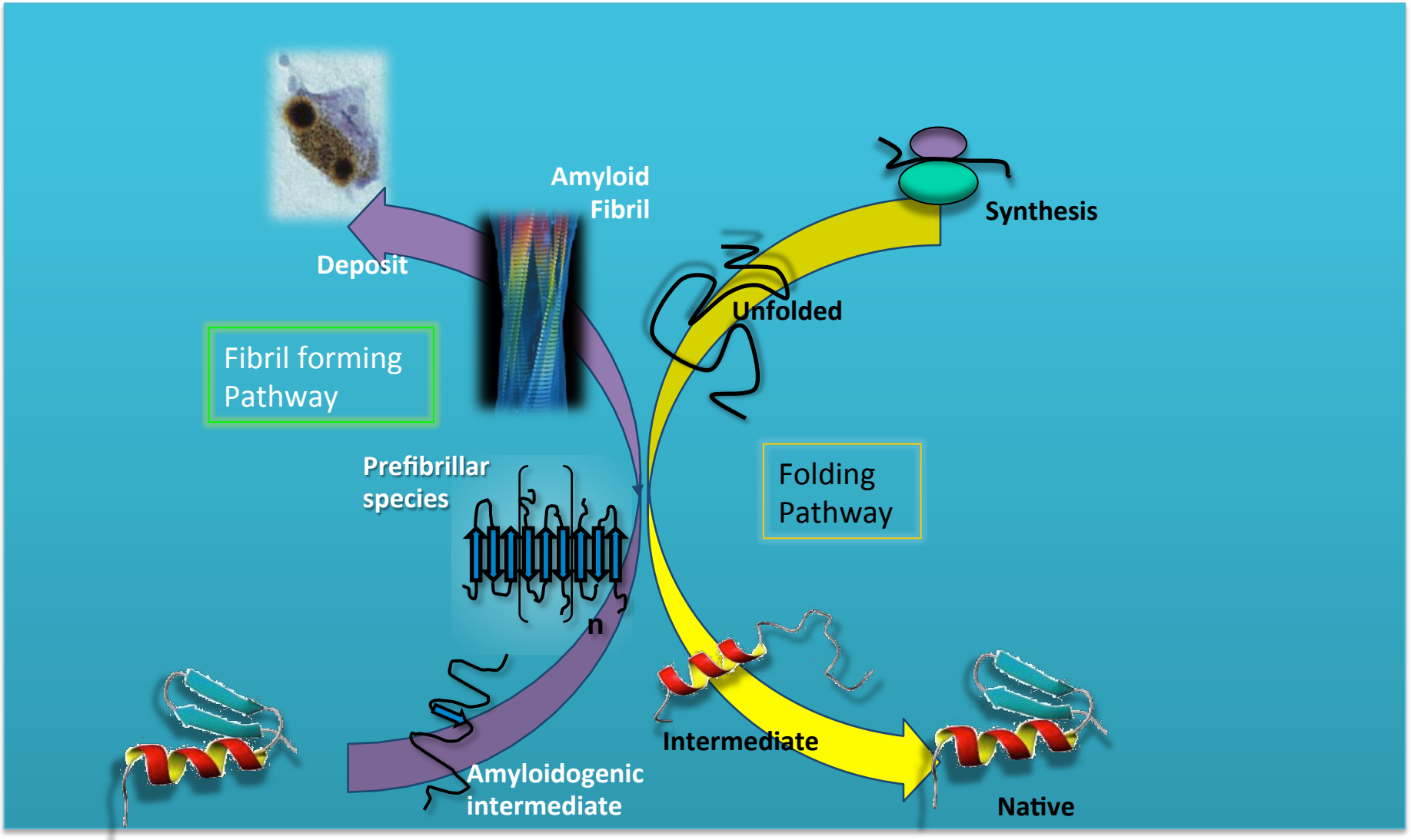
About 600 NDs, 50 million US individuals affected each year.

$100 billion per year is spent on Alzheimer disease (AD) alone (2005) - immense emotional burden on patients and their relatives

As the number of elderly citizens increases, these costs to society also will increase.

Brown et al, Environ Health Perspect. 2005;113, 1250

Protein fibril formation: Hallmark of neurodegenerative diseases



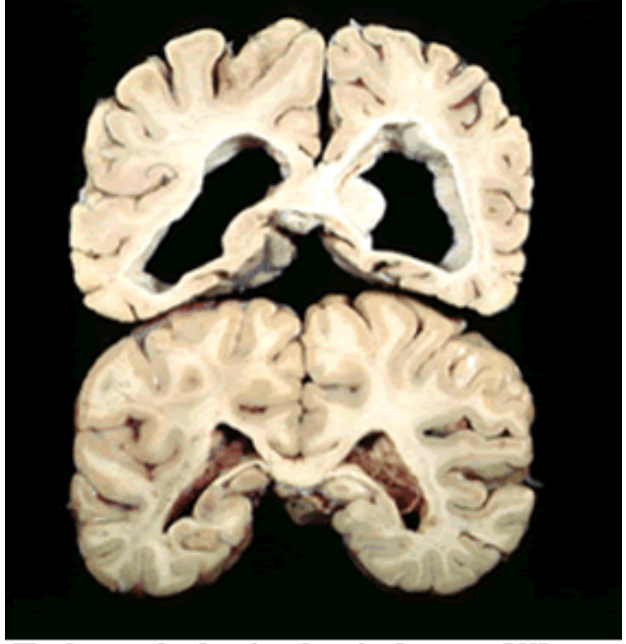
Huntington's disease

- Inherited fatal neurodegenerative disorder

- Over 10,000 people in the western world

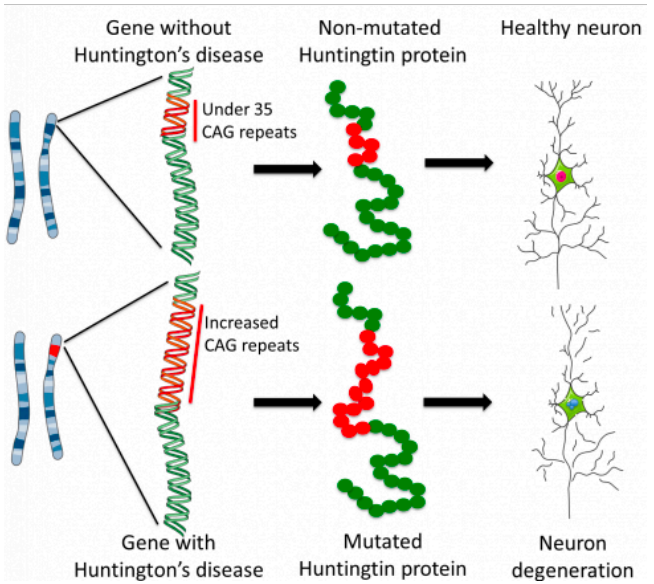
  –Uncontrolled mood swings

- No treatment



The human brain, showing the impact of HD on brain structure in the basal ganglia region of a person with HD (top) and a normal brain (bottom).

http://kobiljak.msu.edu



RNA as a target?

Huntington's disease

↓

CAG repeats

↓

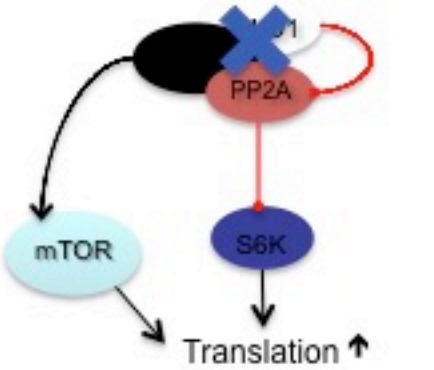
Elongated RNA

↓

Pathogenic RNA_{CAG}/ protein complex

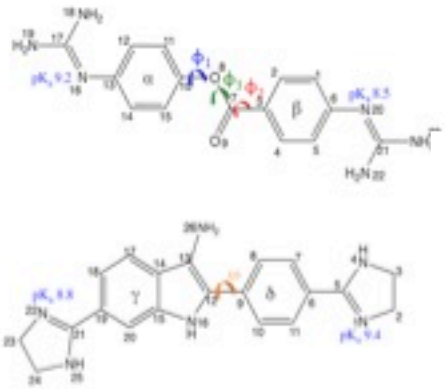
Inhibition

Activation



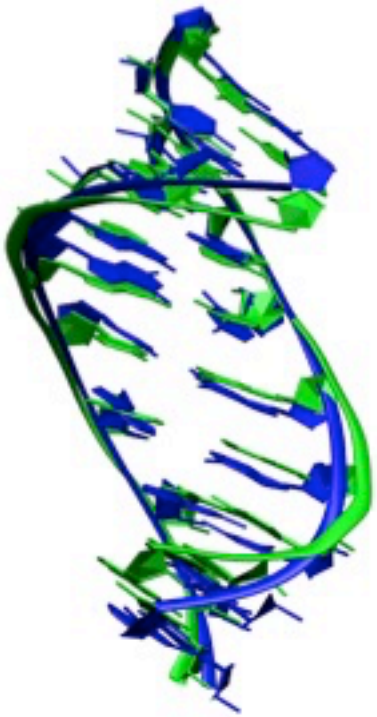
Krauß, Grieshe, Jastrzebska, Chen, Rutschow, Achmuller, Dorn, Boesch, Lukowski, Wanker, Schneider, Schweiger (2013) *Nat. Comm*, 4:1511

K_b (nM)
60± 30



K_b (nM)
700± 80

Kumar *et al.* (2012) ACS Chem Biol. **24**:496.rna



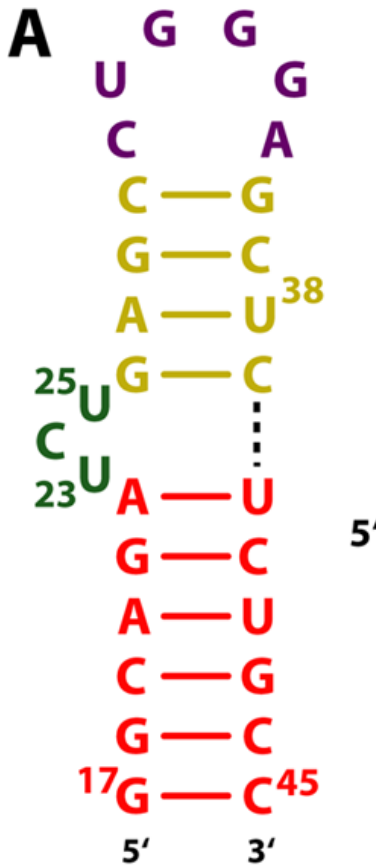
$(r(5'\text{-}G_1GCAGCAGCC_{10})_2$

Kiliszek, *et al. Nucleic Acids Res.* **2010**, *38* , 8370

Test system:

HIV-1 transactivation responsive RNA (TAR)

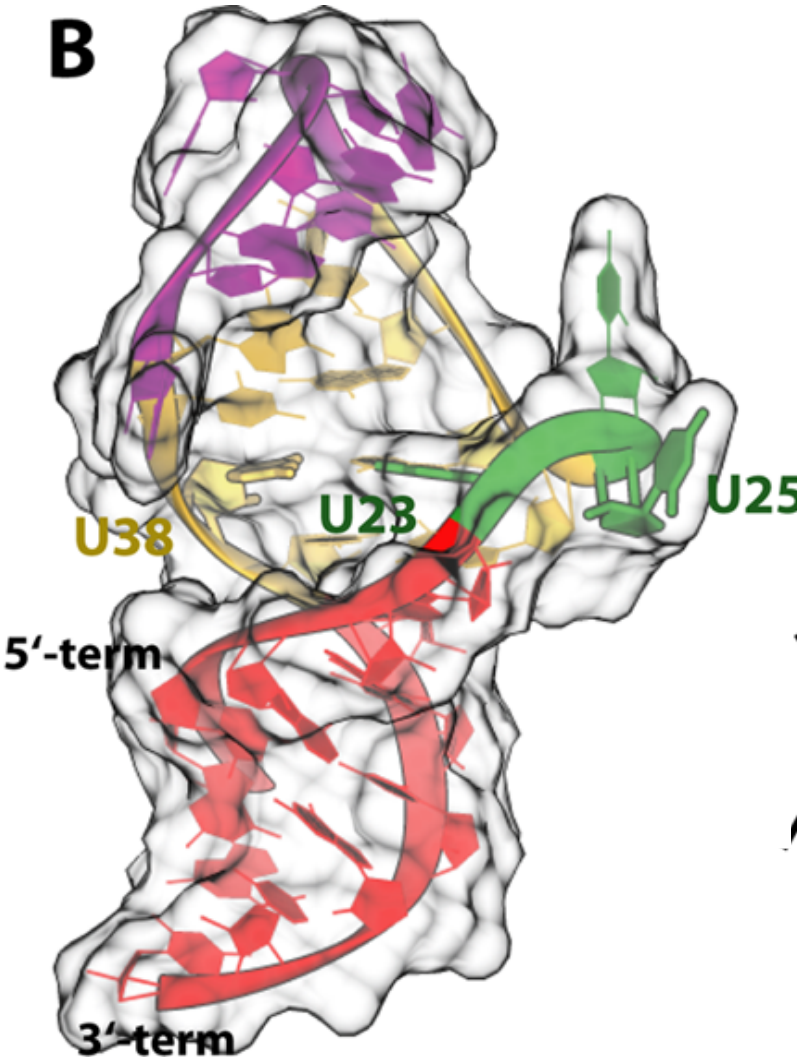
- 59 nucleobase TAR activates elongation of transcription of the integrated virus by forming a complex with the virally encoded HIV-1 Tat protein and with human cyclin T1



Frankel Curr. Opin. Genet. Dev. 1992, 2, 293.
Weeks et al., Science 1990, 249, 1281.
Churcher, et al. J. Am. Chem. Soc. 2010, 132, 17643.
Wang et al. Med. Chem. 2009, 9, 379.
Kikuta, et al. E. J. Am. Chem. Soc. 2001, 123, 7911.
Sztuba-Solinska et al. J. Am. Chem. Soc. 2014, 136, 8402.

Structure: The Bulge

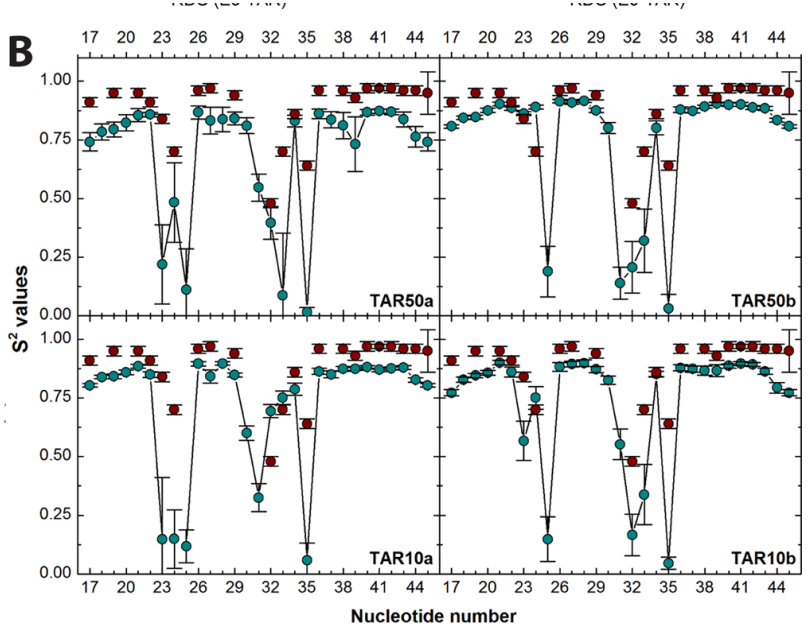
- NMR shows that TAR binds to Tat mimics and small ligands mostly through its “bulge” separating two helical regions (“upper” and “lower” stems). Partial stacking of U23 on A22 and C24 on U23 in the bulge generates a kink between the two stems

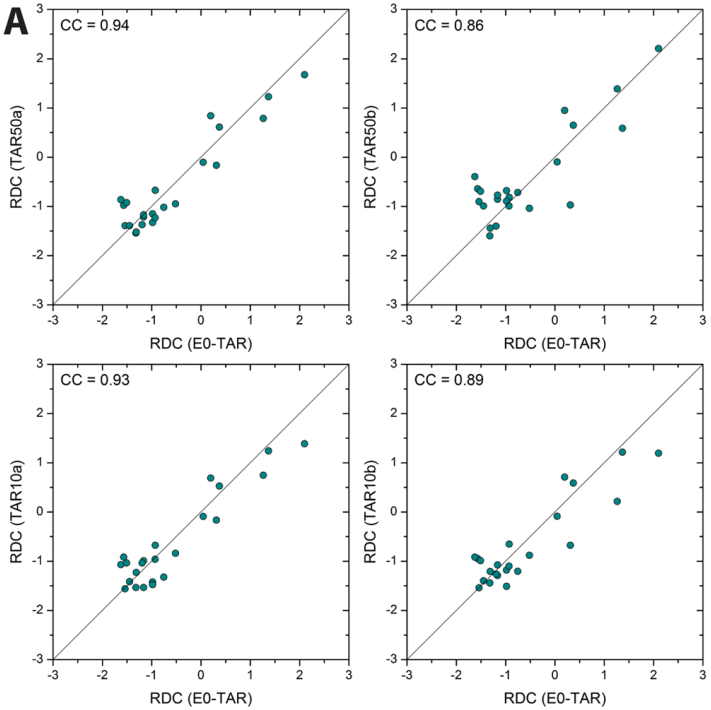


Aboul-ela et al. J. Mol. Biol. 1995, 253, 313,
Aboul-ela et al Nucleic Acids Res. 1996, 24, 3974.
Faber et al. J. Biol. Chem. 2000, 275, 20660.
Du et al. Chem. Biol. 2002, 9, 707.
Murchie et al. J. Mol. Biol. 2004, 336, 625.
Davis et al. J. Mol. Biol. 2004, 336, 343.
Davidson et al. Proc. Natl. Acad. Sci. U. S. A. 2009, 106, 11931, Nucleic Acids Res. 2011, 39, 248
J. Mol. Biol. 2011, 410, 984.

Investigating TAR internal motion

- Several μs-long NPT AMBER-based MD simulations starting from *apo* and *holo* TAR give similar results





Perez, et al. Biophys. J 2007, *92*, 3817.

Zhang et al. J. Am. Chem. Soc. 2003, 125, 10530.

Musiani et al, *JACS* 2014, 136, 15631

Free energy as a function of selected collected variables

1. Distance between the centers of mass of the ligand and of the CAG tract in RNA_{10}

2. Number of H-bonds between the ligand and the RNA

3. Number of hydrophobic contacts between the ligand and the RNA

Step I: Binding of known ligands

JÜLICH FORSCHUNGSZENTRUM

Huntington's disease:
Repeat expansion-based disease

CAG repeats fold into expanded hairpins
(disease threshold:> 37 repeats)

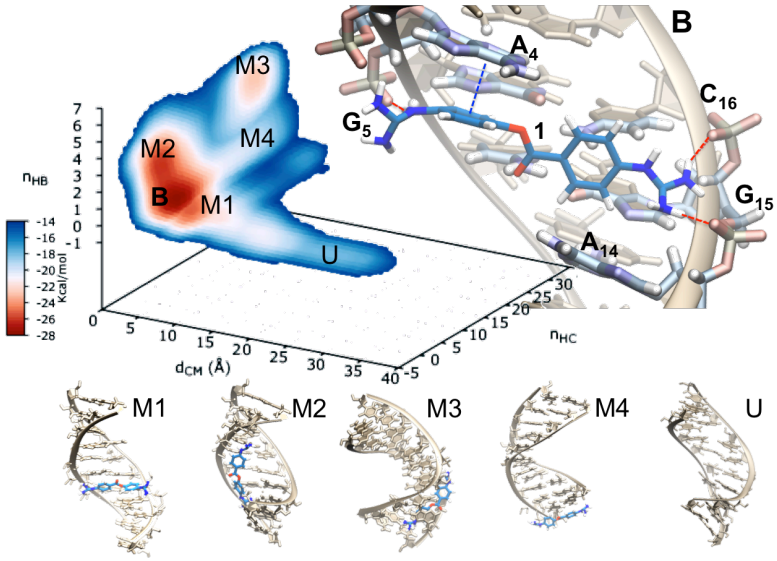
↓

Pathogenic RNA_{CAG}/protein (e.g MID1) complex

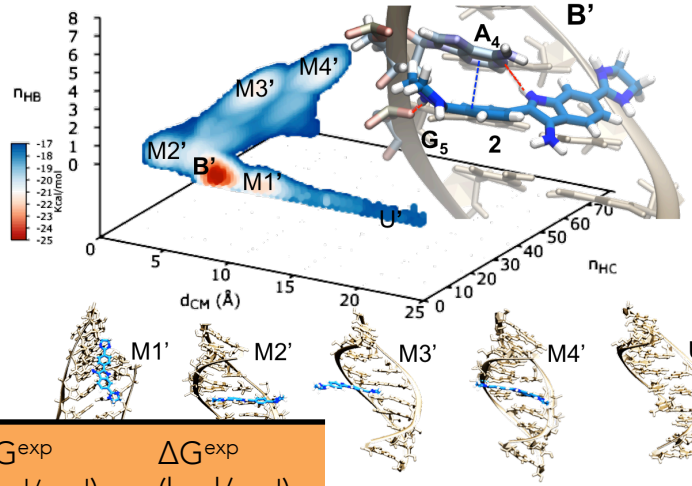
↓

Increased translation of neurotoxic HTT protein

Derive small molecules to target $(CAG)_n$



MD+ Well-Tempered Metadynamics



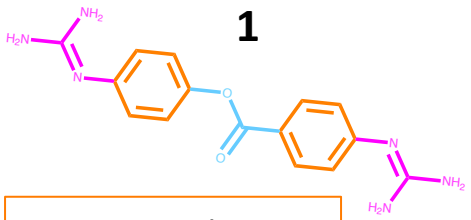
	ΔG^{exp} (kcal/mol)	ΔG^{exp} (kcal/mol)
1	-9.8±0.7	~-10
2	-8.4±0.4	~-8

Bochicchio A., Rossetti G., Tabarrini O., Krauß S. , Carloni P. *J.Chem.Theory Comput.*, 2015, 11 (10), pp 4911-4922

Step II: Identification of new compounds

JÜLICH FORSCHUNGSZENTRUM

Scifinder database search

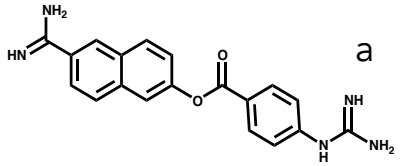


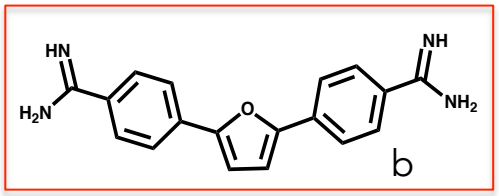
Two aromatic rings interact with Adenines base

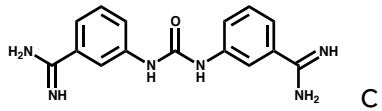
Protonable moieties

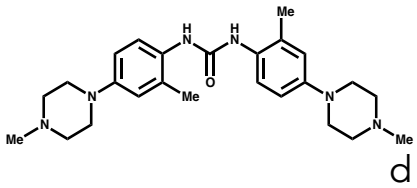
Linker: e.g. amide, urea,furan ketone

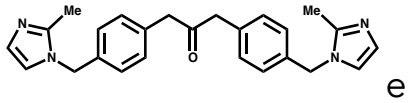
25 compounds selected





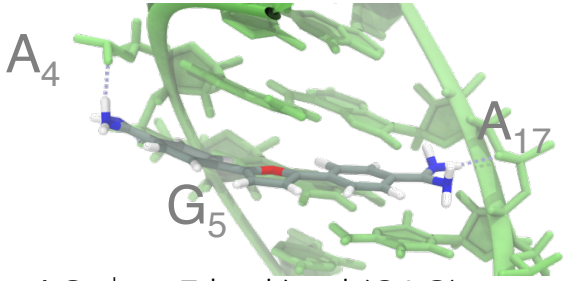






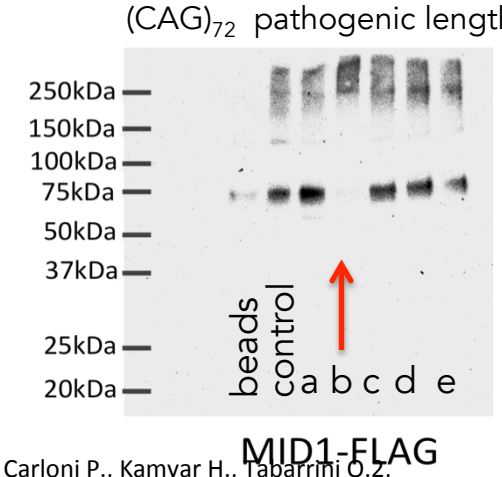
5 *In vitro/in cell* essays

✓ Binds to CAG motif



ΔG^{calc} ~ 7 kcal/mol $(CAG)_2$
ΔG^{MST} = 5.7± 0.2 kcal/mol $(CAG)_{18}$
ΔG^{MST} = 5.1±0.1 kcal/mol $(CAG)_{40}$

✓ Inhibits the binding of proteins (e.g. MID1) to (CAG)n *in vitro and in HD cell models*



Matthes F.#, Massari S.#, Bochicchio A.#, Schorpp K.#, Schilling J.#, Weber S., Offermann N., Desantis J., Wanker E., Carloni P., Kamyar H., Tabarrini O.Z., Rossetti G., Krauß S., submitted to Sci. Rep.

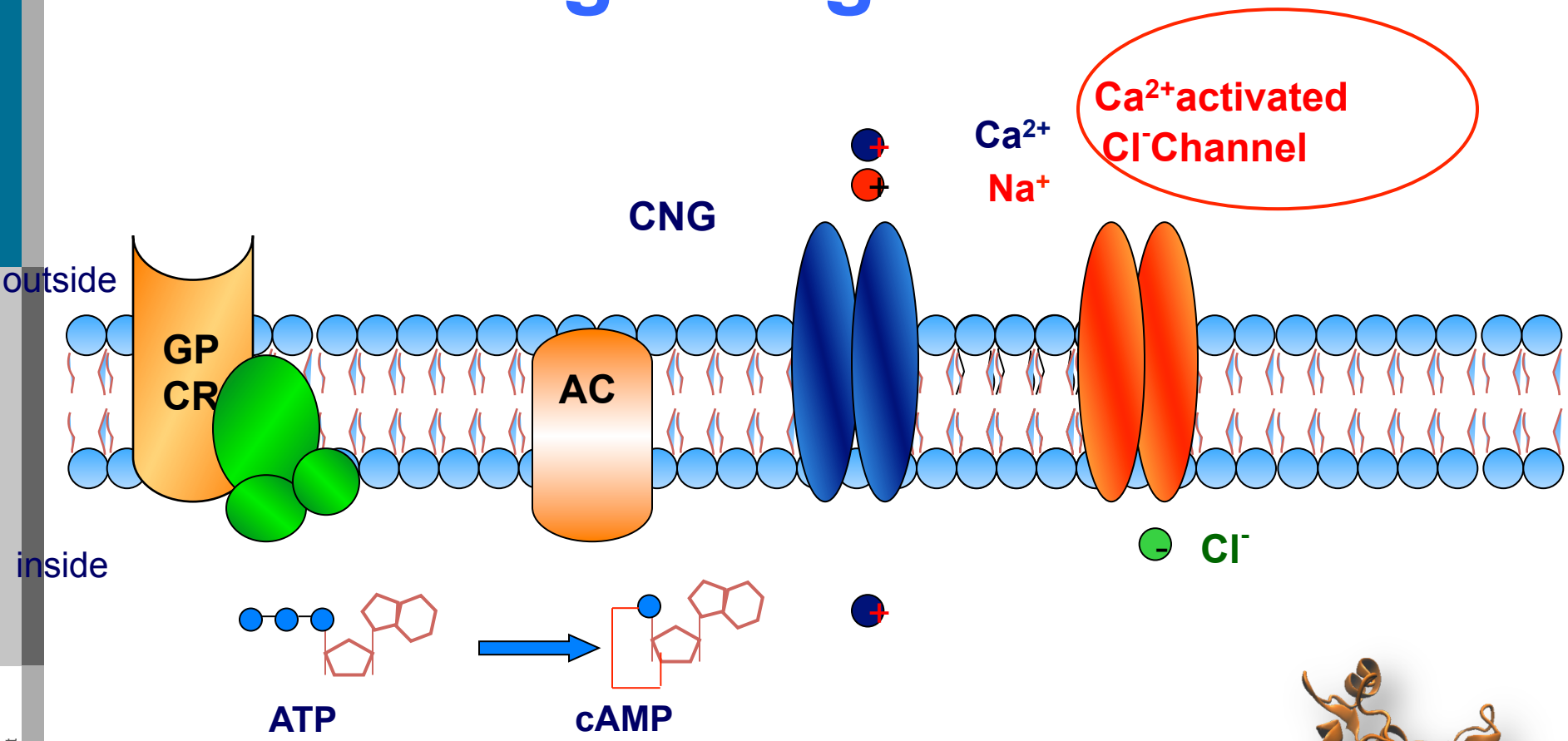
Acknowledgements

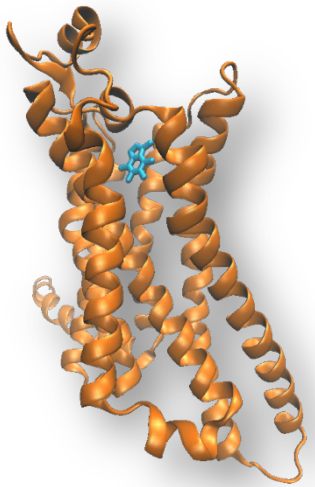
Vania Calandrini, Alejandro Giorgetti, Massimo Sandal, Xevi Biarnes, Michael Leguebe, Giulia Rossetti, Mercedes Alfonso Prieto, Luca Maggi, Xiaojing Cong, Fabrizio Fierro, Anna Bochicchio
Prof Meyerhof's group (German institute of Nutrition, Potsdam, Germany),
Prof. Katrin Amunts (FZJ)
Prof. Sven Cichon (FZJ)
Prof. Andreas Bauer's (FZJ)
Prof. B. Neumeier (FZJ)
Prof. Sybille Krauss (DNZE, Bonn)

, May 2017

Funding: DFG, BMBF, Ernesto Illy Foundation, Human Brain Project, JARA, BioExel, HPC Leap

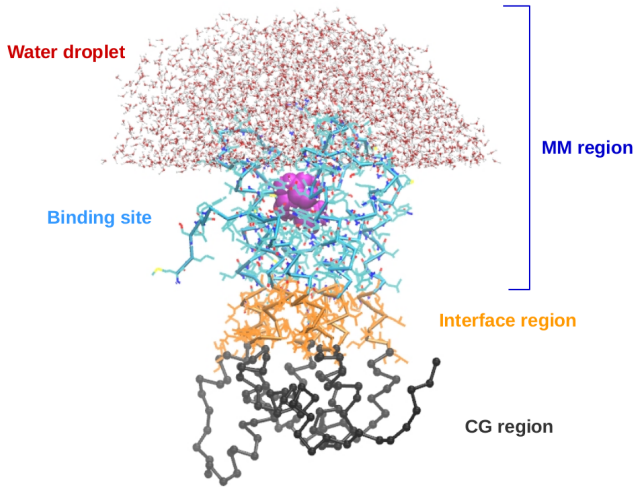
GPCR's signaling cascade





A multiscale approach for drug-affinity predictions

Molecular Mechanics/Coarse-grained approach

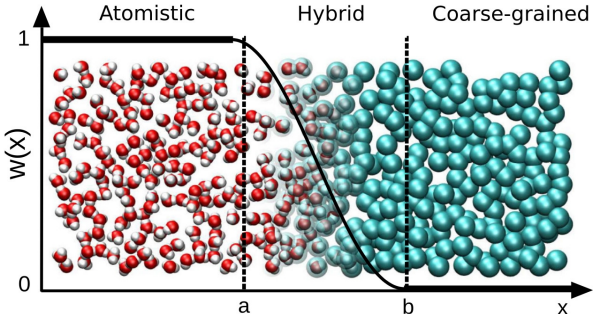


Leguebe M. et al., *PLOS ONE* (2012)

Hamiltonian-Adaptive resolution scheme

$$H = K + V^{p/p-w} + \sum_{\alpha}^{N}\left\{\lambda_\alpha V_\alpha^{MM} + (1-\lambda_\alpha)V_\alpha^{CG}\right\} - \sum_{\alpha}^{N}\Delta H(\lambda_\alpha).$$

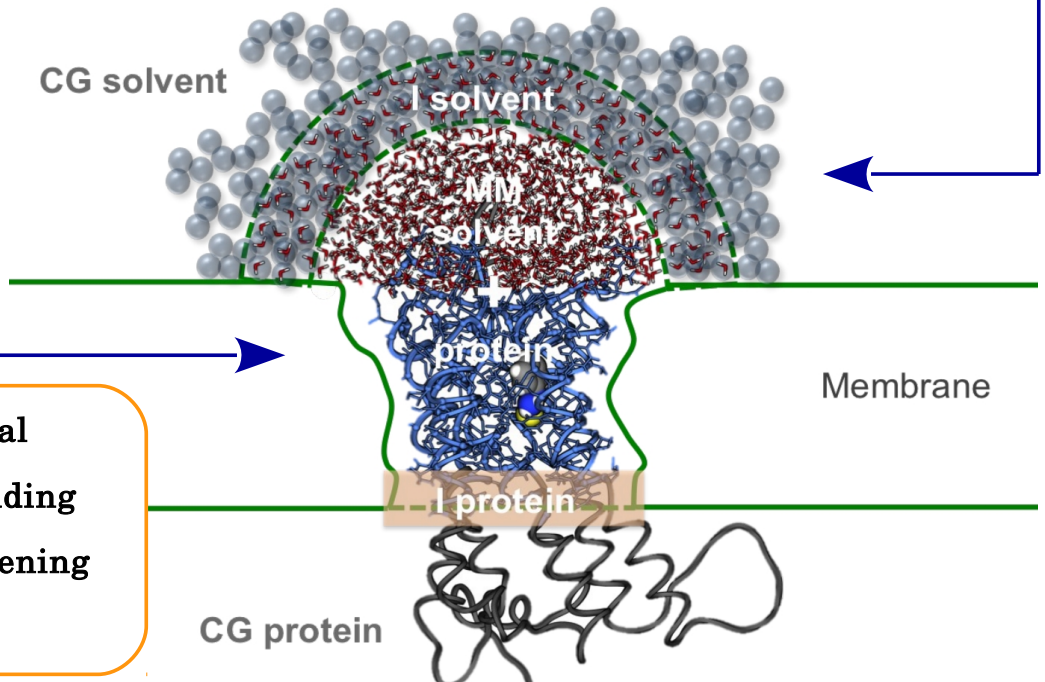
$$\Delta H(\lambda_\alpha) = \frac{\Delta F(\lambda_\alpha)}{N} + \frac{\Delta p(\lambda_\alpha)}{\rho_0} \equiv \Delta\mu(\lambda_\alpha) = \frac{\Delta G(\lambda_\alpha)}{N}.$$



Potestio R. et al., *Phys. Rev. Lett.* (2013)

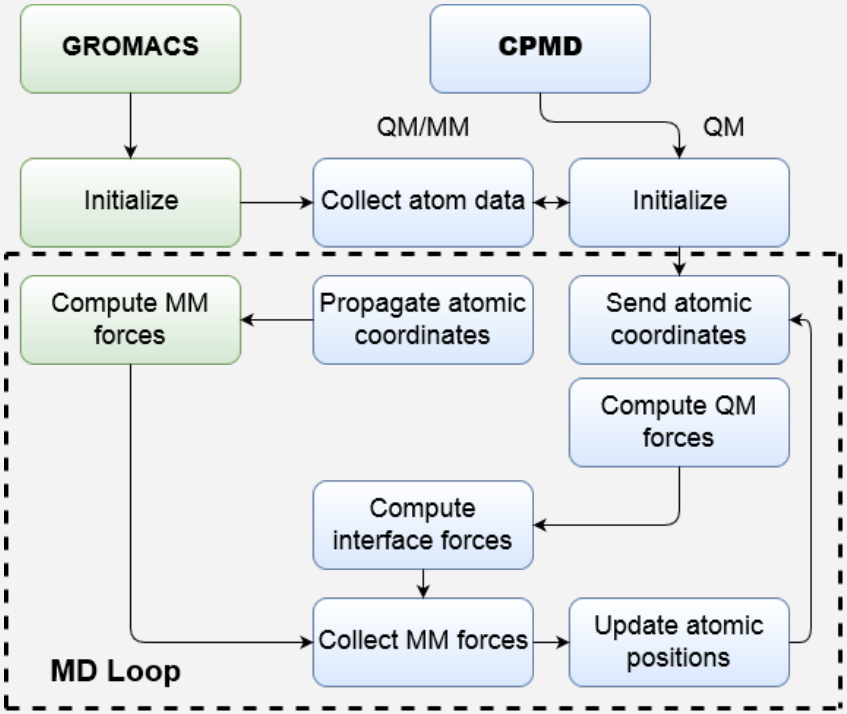
Dual-resolution ***protein***

Dual-resolutio ***solvent***



Simulation of a **grand canonical ensemble** for calculation of **binding free energies** and **ligand screening** (need for **HPC resources**).

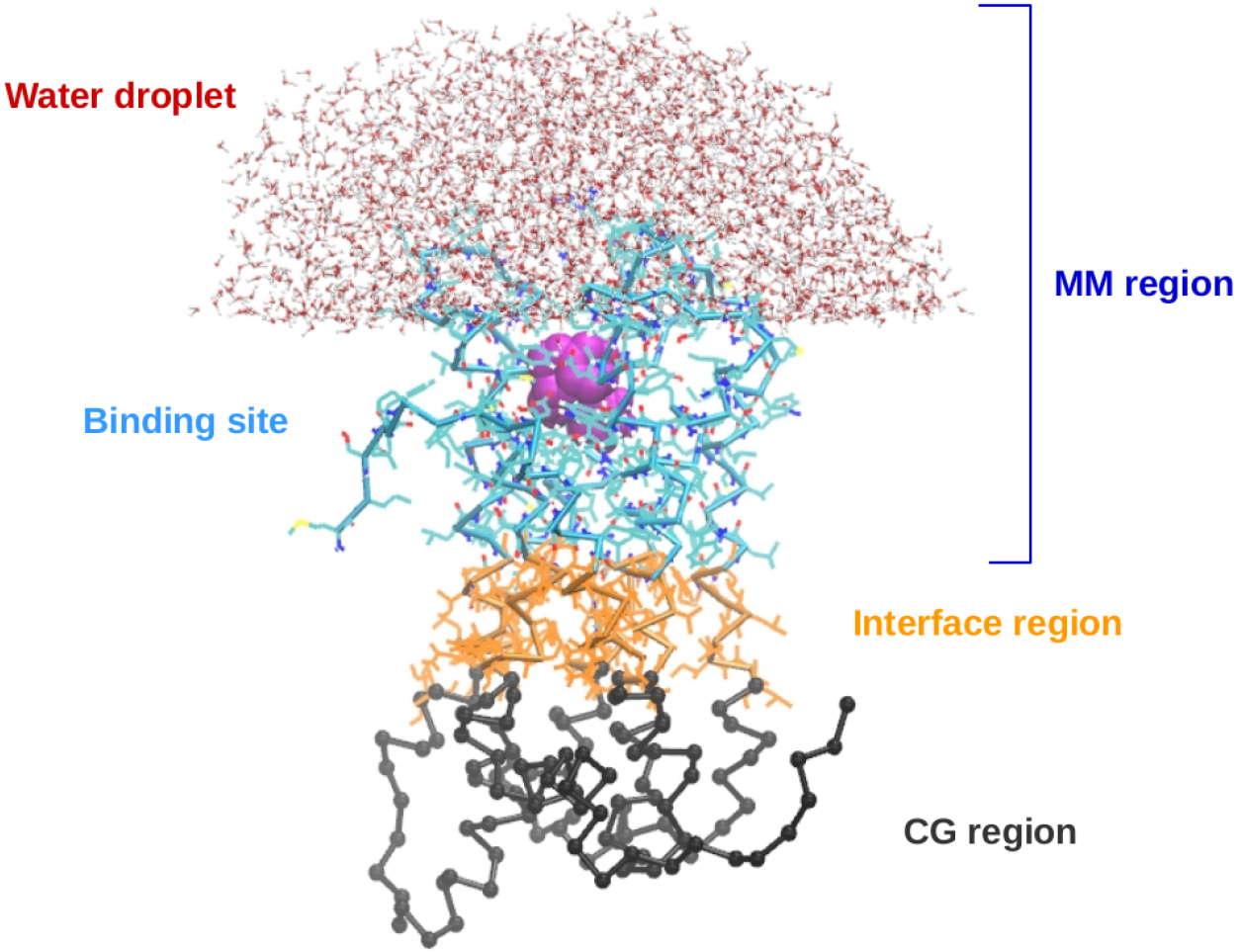
New HPC-based Approach



- Multiple-Program Multiple-Data approach using the ad-hoc communication library
- Fully exploits the efficient parallel architecture of both CPMD and the MM code
- Allows coupling to virtually any MM code

Improving the scaling performance allows getting better sampling

Molecular Mechanics/Coarse-grained approach

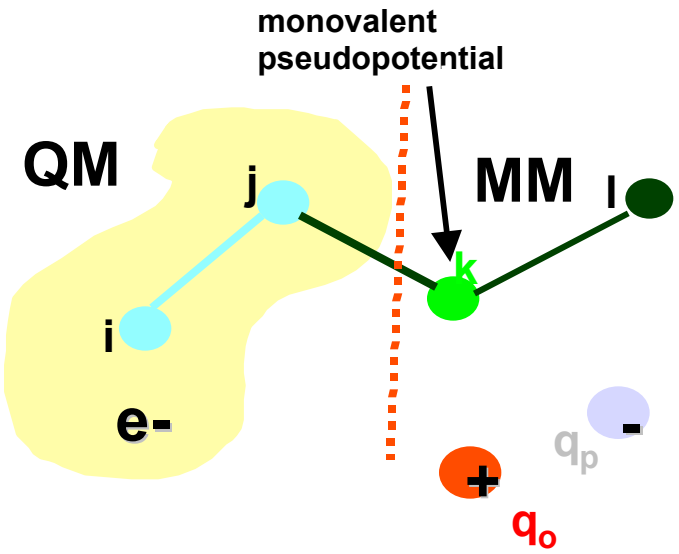


Leguebe M. et al., *PLOS ONE* (2012)

→ Efficient sampling of side chain at binding site

→ Simplified representation of the rest

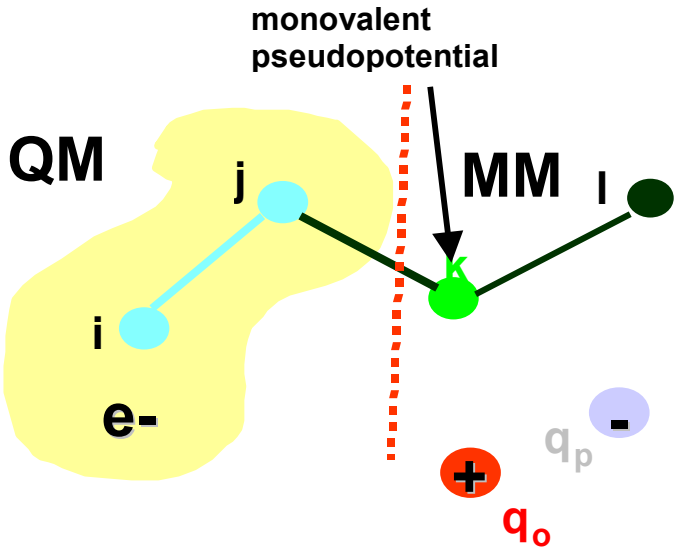
$E_{QM/MM}$:Bonded Interactions

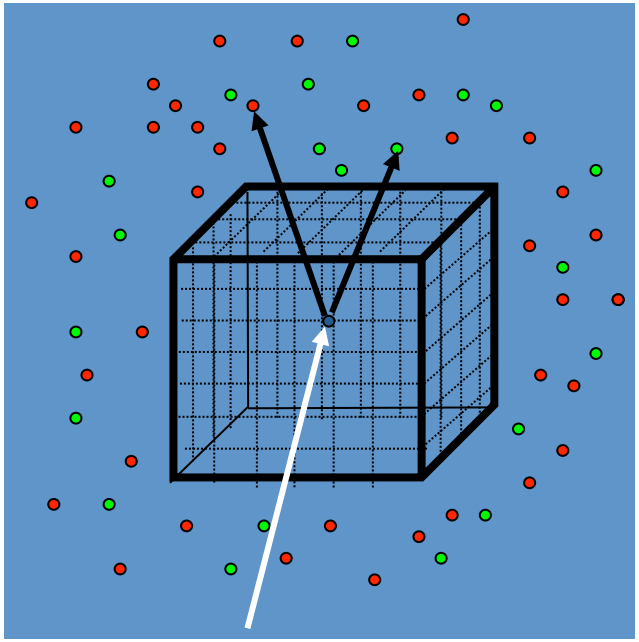


MM atoms/QM atoms bonds: monovalent pseudopotentials

Angle bending and dihedral distorsions:Classical force field

$E_{QM/MM}$:Non bonded interactions



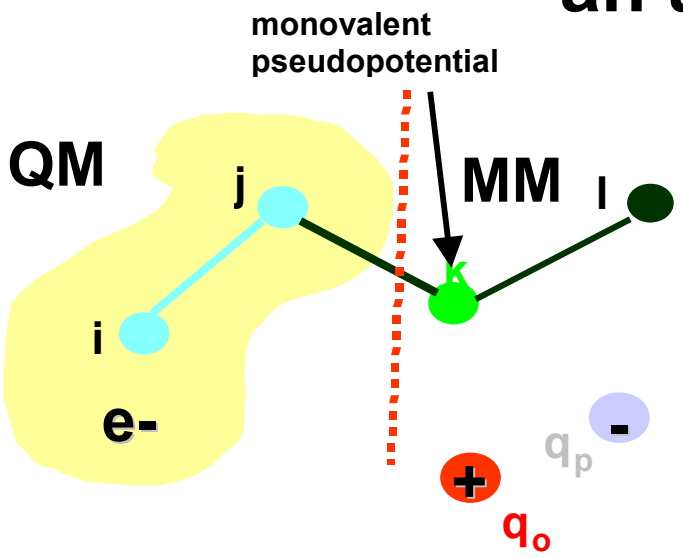


$$E^{st}_{QM/MM} = \sum_{I \in MM} q_I \int dr \rho(r) / |r - R_I| + \sum_{\substack{I \in MM \\ J \in QM}} v_{vdw}(R_{IJ})$$

1-Electron density is overpolarized at short range: *electron spill-out* problem

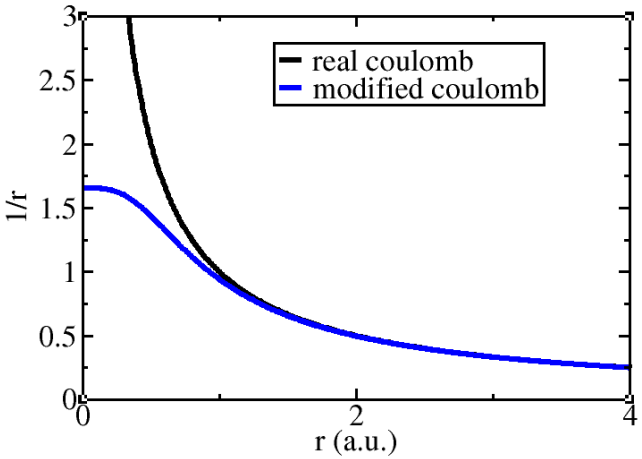
2- # operations ~N_{rsgrid} x N_{MM} ~1,000 x 10,000

1-Spill out: Replacing the Coulomb potential with an *ad hoc* function



$$E^{ele}_{QM/MM} = \sum_{i \in MM} q_i \int dr \rho(r) v_i(|r - r_i|)$$

$$v_J(r) = \frac{R_{cJ}^4 - r^4}{R_{cJ}^5 - r^5}$$



R_{CJ}=cutoff radii, tested in Laio et al JCP 2002

each node with descendants represents the inferred most recent common ancestor of the descendants, and the edge lengths in some trees may be interpreted as time estimates. Each node is called a taxonomic unit. Internal nodes are generally called hypothetical taxonomic units, as they cannot be directly observed.