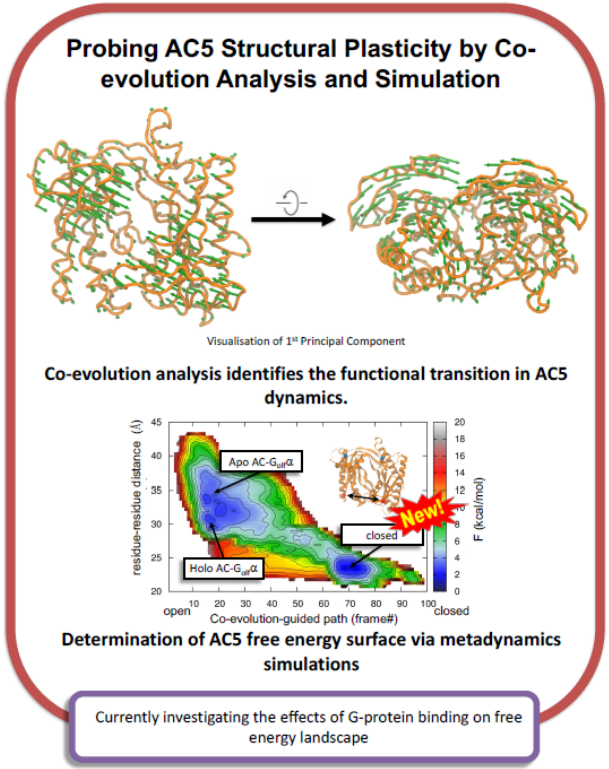
HBP Highlight

SP6



The regulation of AC(5) by G-protein from coevolution-driven molecular simulations

→ Characterization of ACs intrinsic dynamics

→ Identification of a NEW, previously uncharacterized, closed state.

→ Regulation of AC dynamics by G-proteins

HBP Highlight

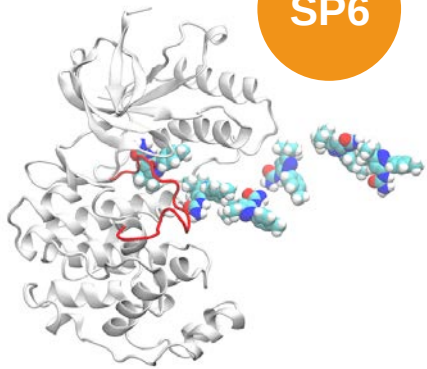
SP6

Platform for atomistic MD simulations of signal-transduction proteins in the brain

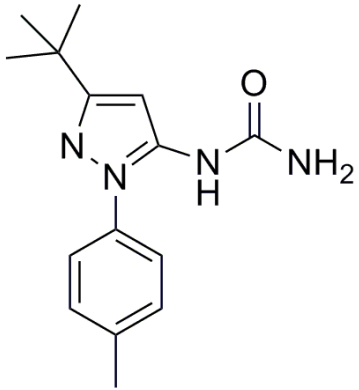
- Web-based platform to allow access to molecular dynamics (MD) simulations of complex systems involved in signal transduction in the brain.
- Hundreds of trajectories obtained by means of state-of-the-art atomistic MD simulations in near-physiological conditions for ligand- and voltage-gated ion channels, G-protein coupled receptors and nuclear hormone receptors.
- The platform shall provide advanced tools to analyze trajectories mimicking the procedures followed by human experts.

HBP Highlight

SP6



- Ligands' unbinding constants (k_{off}): key quantities for neuroimaging experiments and for neuropharmacology
- Predicting accurately k_{off} is difficult, yet it could help design molecules with improved residence time
- Novel molecular simulation methods reproduce k_{off} in a test ligand/protein system. We are applying now this technique to neuroreceptors of interest for HBP

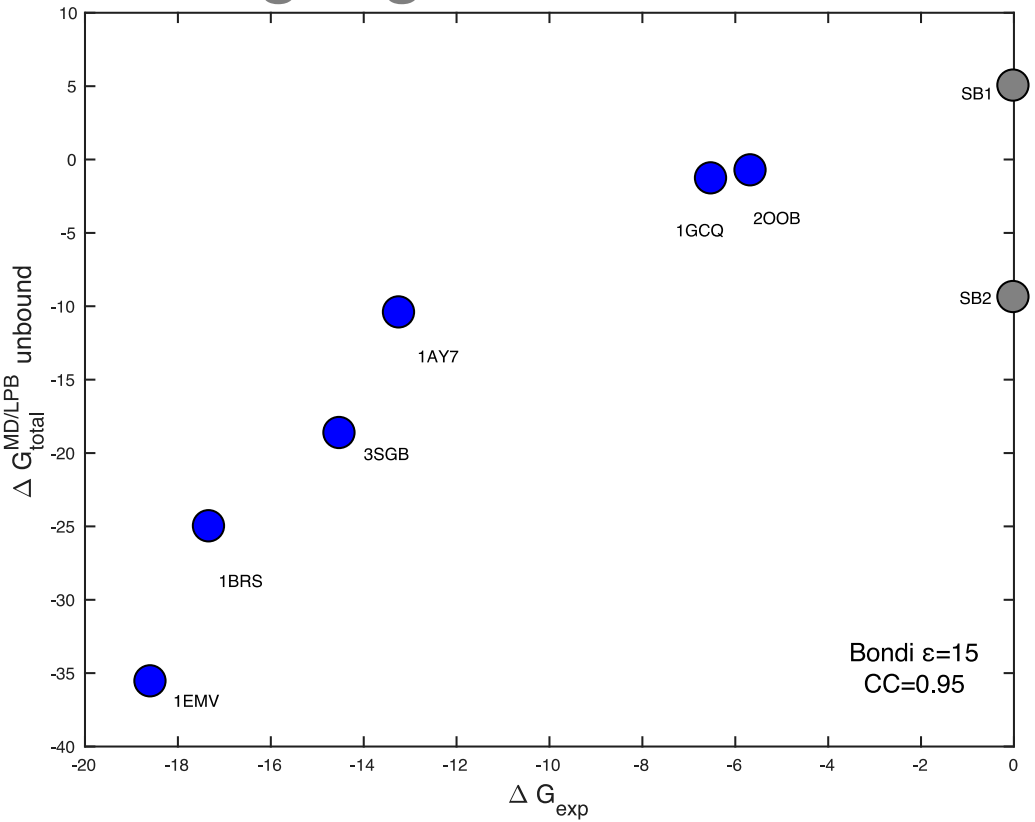


	k_{off} (s^{-1})
Experimental[1]	0.14
Calculated	0.02 ± 0.01

Casasnovas-Perera et al, J.Am.Chem. Soc. 2017

HBP Highlight

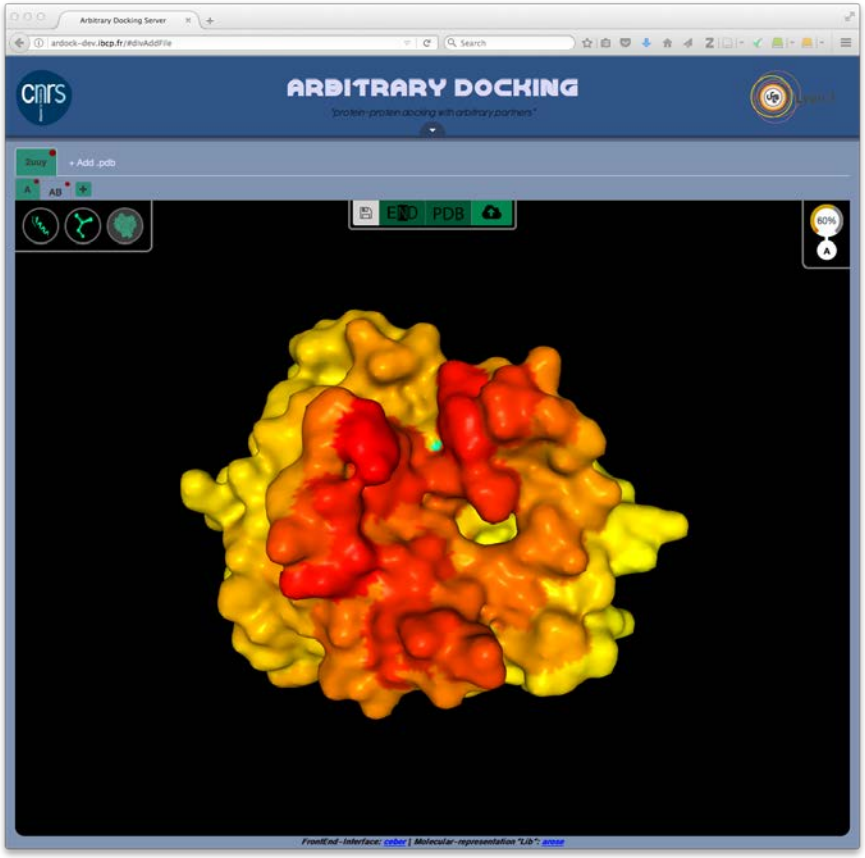
SP6



→ Molecular dynamics simulations and continuum electrostatics can be used to predict protein-protein binding affinities with high correlation

HBP Highlight

SP6



→ Structural matching with multiple probes can highlight preferred regions of interaction from isolated structures

HBP Highlight

FHF-independent conduction of action potentials along the leak-resistant cerebellar granule cell axon

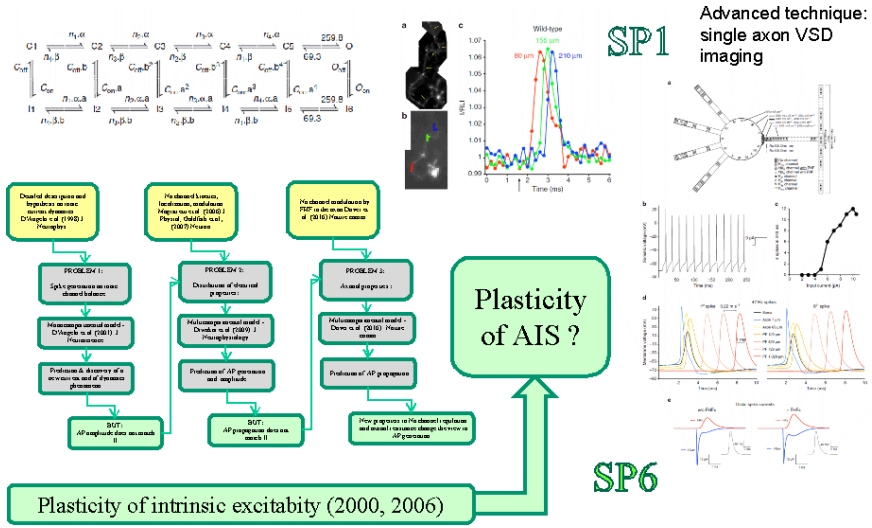
SP6

Katarzyna Dover[1,2], Christopher Marra[1,3], Sergio Solinas[4,†], Marko Popovic[5,†], Sathyaa Subramaniyam[6], Dejan Zecevic[5], Egidio D'Angelo[4,6] & Mitchell Goldfarb[1,3]

Dover et al., 2016, *Nature Communications* Vol. 7, 12895
http://www.nature.com.bibliosan.clas.cineca.it/articles/ncomms12895

Dover et al. used multicompartmental modeling to analyze the spike generation and conduction properties in central mammalian axons, uncovering unusual passive and active properties

- experimental measurements using single cell voltage-sensitive dye imaging revealed quasi-infinite resistance in the axon.
- Immunostaining revealed that FHF+ Na channels are enriched in the initial segment while FHF- Na channels are located in the axon.
- In a detailed granule cell model, these properties allowed energy-less action potential propagation at constant speed.
- In conclusion, axonal conductance in central mammalian neurons is a specialized process that extends the classical Hodking-Huxley theory.



Dover, ... D'Angelo, Goldfarb, Nature Comm. 2016

HBP Highlight

Rich cell-type-specific network topology in neocortical microcircuitry

Eyal Gal[1,2]

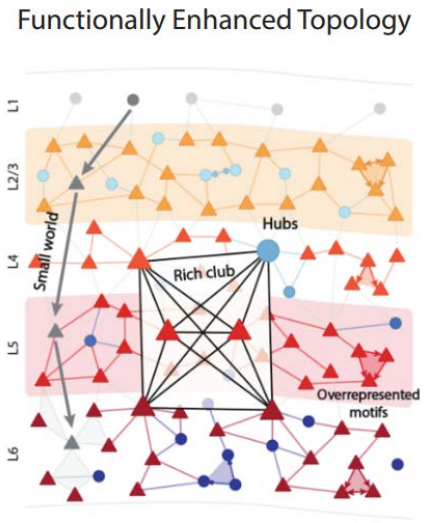
SP6

Gal et al., 2017, *Nature Neuroscience* Vol. 20, No. 7, pp 1004-113

http://www.nature.com/neuro/journal/v20/n7/full/nn.4576.html?foxtrotcallback=true

Gal et al. used graph theory to analyze the topology of detailed computer- reconstructed cortical microcircuits, uncovering highly non-random features of this circuit

- A small-world topology was found with an average of 2.5 synapses separating any two cells
- Pyramidal neurons maintained relatively constant excitation/inhibition ratios.
- The circuit contained highly connected hub neurons and forming an interconnected cell-type-specific rich club.
- Certain three-neuron motifs were overrepresented, matching recent experimental results.



HBP Highlight

FHF-independent conduction of action potentials along the leak-resistant cerebellar granule cell axon

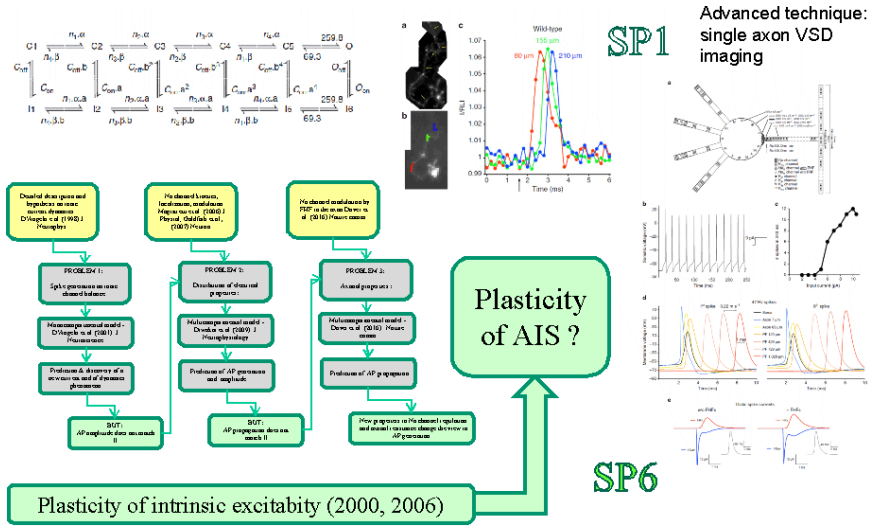
SP6

Katarzyna Dover[1,2], Christopher Marra[1,3], Sergio Solinas[4,†], Marko Popovic[5,†], Sathyaa Subramaniyam[6], Dejan Zecevic[5], Egidio D'Angelo[4,6] & Mitchell Goldfarb[1,3]

Dover et al., 2016, *Nature Communications* Vol. 7, 12895
http://www.nature.com.bibliosan.clas.cineca.it/articles/ncomms12895

Dover et al. used multicompartmental modeling to analyze the spike generation and conduction properties in central mammalian axons, uncovering unusual passive and active properties

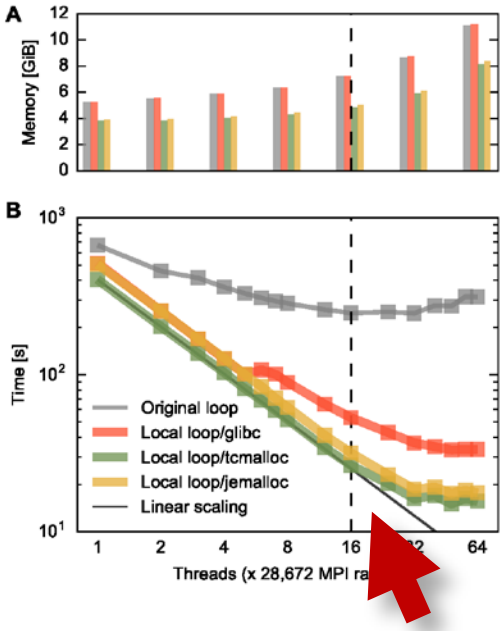
- experimental measurements using single cell voltage-sensitive dye imaging revealed quasi-infinite resistance in the axon.
- Immunostaining revealed that FHF+ Na channels are enriched in the initial segment while FHF- Na channels are located in the axon.
- In a detailed granule cell model, these properties allowed energy-less action potential propagation at constant speed.
- In conclusion, axonal conductance in central mammalian neurons is a specialized process that extends the classical Hodking-Huxley theory.



Dover, ... D'Angelo, Goldfarb, Nature Comm. 2016

SP6 T6.3.5: NEST Technology

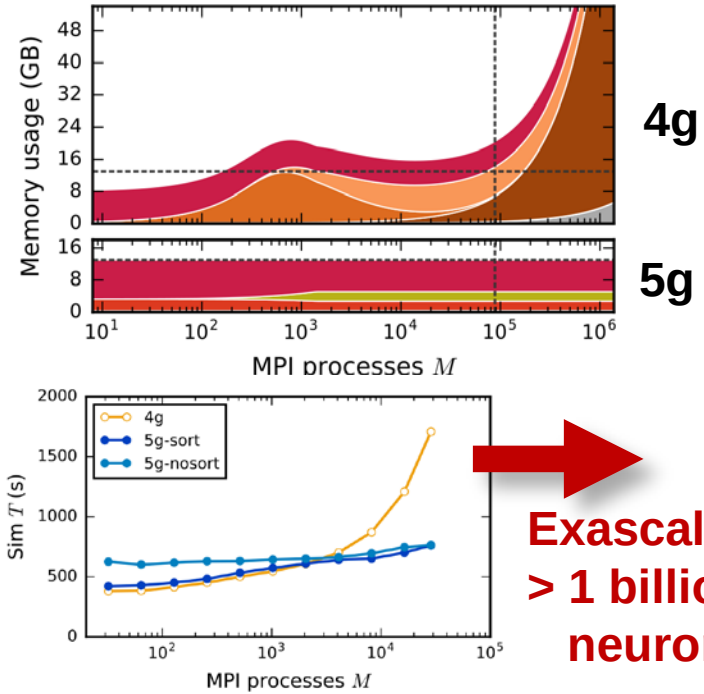
Fast massively parallel network construction



Rat-brain sized model built in 20 seconds

Ippen et al (2017)

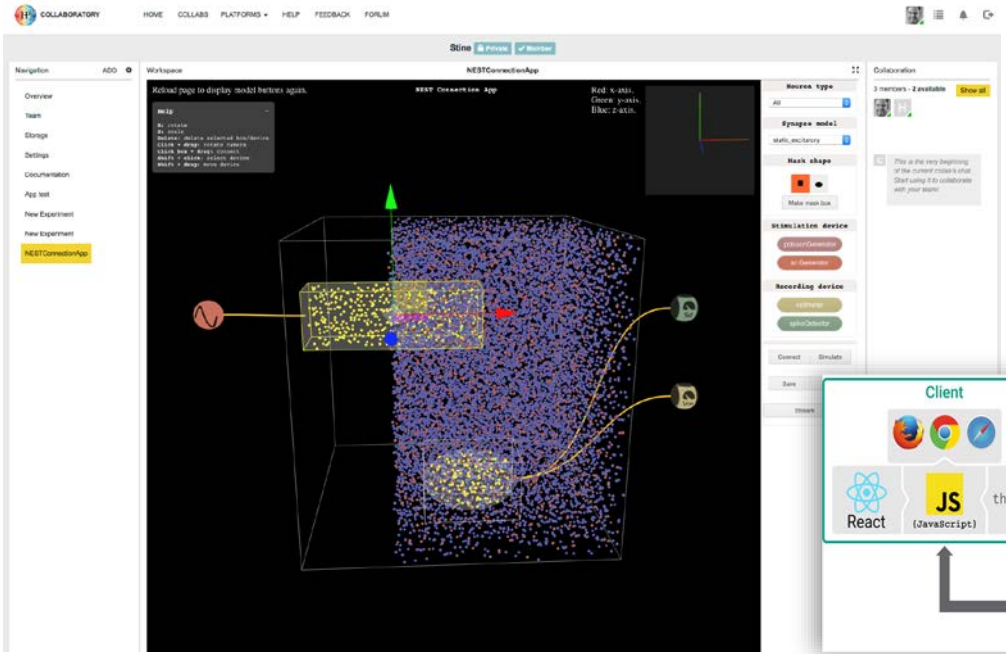
Two-tier connection infrastructure for exascale systems

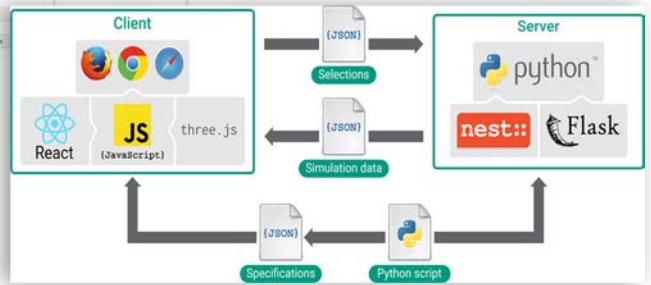


Exascale, > 1 billion neurons

Jordan et al (2017), in prep.

NEST Instrumentation App





- Connect recording and stimulation devices to networks via GUI
- Device connections transmitted to NEST for instantiation and simulation
- GUI runs locally in Collaboratory, NEST on remote HBP resource