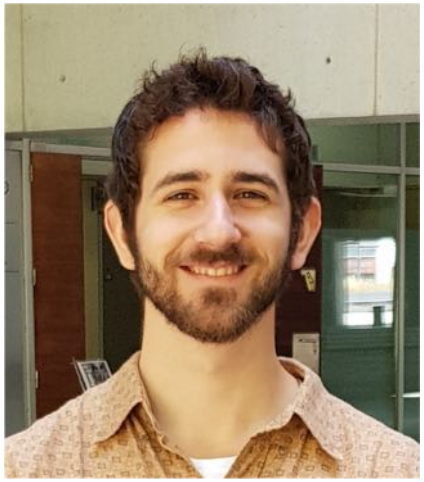
Webinar

CompBioMed
A Centre of Excellence in Computational Biomedicine

Webinar #5
High Throughput Molecular Dynamics for Drug Discovery

25 October 2018



Speaker: **Adrià Pérez** (UPF)

The webinar will start at 12pm CEST

Moderator: **Ben Czaja** (UvA)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 675451

The series is run in collaboration with: VPH Institute Building the Virtual Physiological Human

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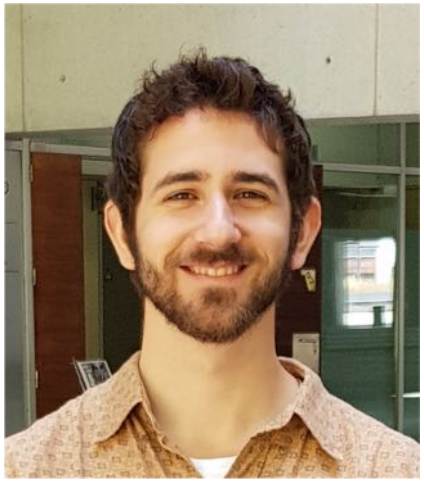

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Welcome!

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Overview

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- Introduction
  - Drug Discovery
  - MD simulations
  - Computer-aided Drug Discovery
- MD Simulations: State of the art
  - Decreasing computational cost of MD
  - Markov State Models
  - Adaptive Sampling
- Example case: Benzamidin-Trypsin
  - System preparation
  - Setting up simulations
  - Analysis: Predicting affinity

Drug Discovery

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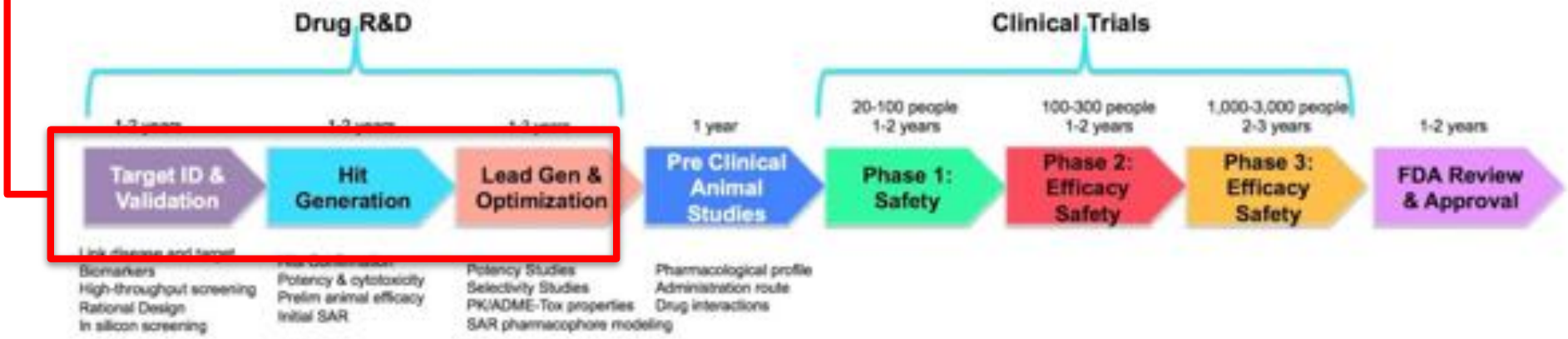
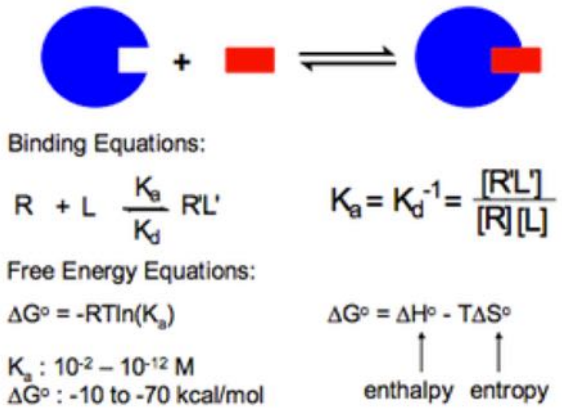
- The process in which new medications (drugs) are discovered.
- Drugs act on biological targets (normally proteins) by binding to them to change their behaviour or function.
- The Drug R&D is mostly done *in vitro* and *in silico*.
- *In silico* approaches can be used in all the three initial stages of Drug Discovery.

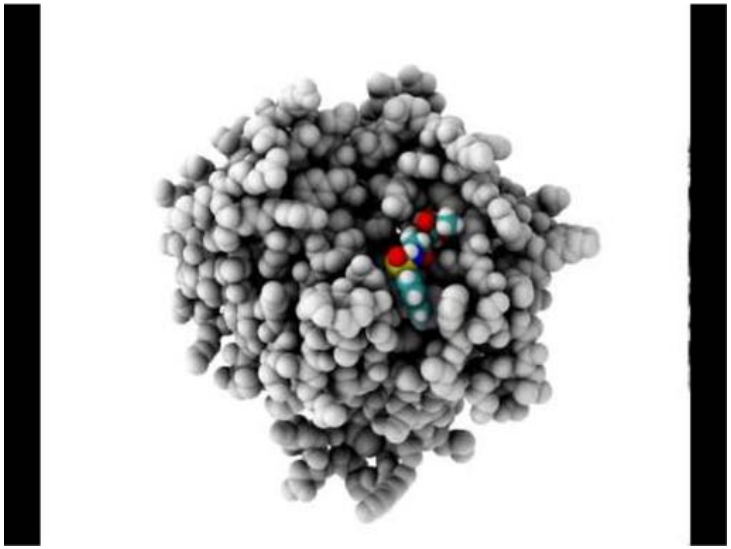


Protein-ligand binding

- One of the goals in the first stages of drug discovery is to predict whether a **given molecule** will **bind** to a **target** and, if so, how strongly (and how fast).
- Macroscopic physical properties can be calculated from the microscopic binding process.



Thermodynamics of binding (taken from https://dsdht.wikispaces.com/)



Depiction of a binding event (taken from https://www.youtube.com/user/ps3grid)

Molecular Dynamics simulations

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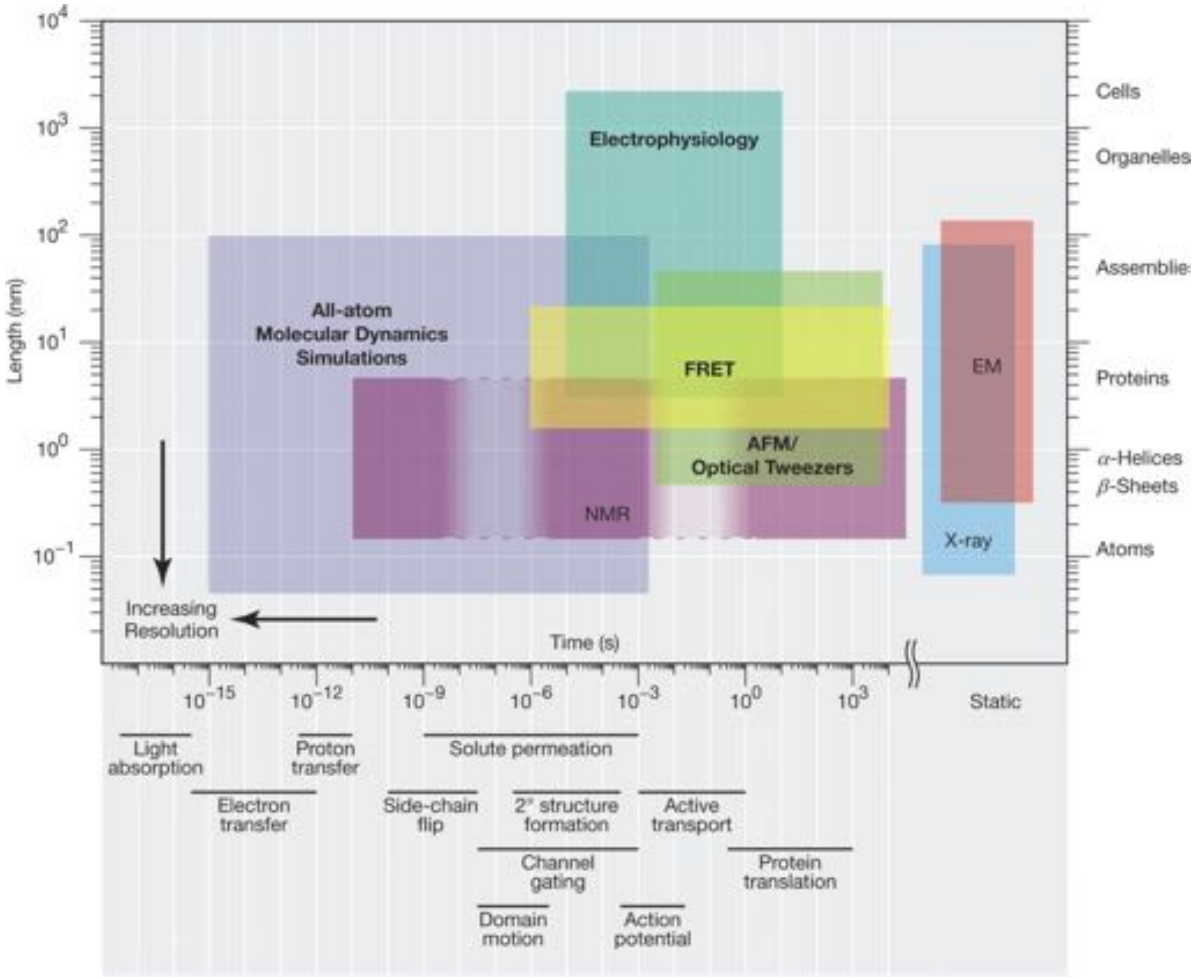
- Molecular Dynamics (MD) is a computational method that allows us to **simulate** an **atomic model** of the system of interest (e.g. protein-ligand binding).
- Simulations allows us to observe the mechanical movement of the system **along time.**
- From an MD trajectory, one can extract both **strucutral** and **kinetic** information with high accuracy.



MD: Molecular Mechanics

Force-fields

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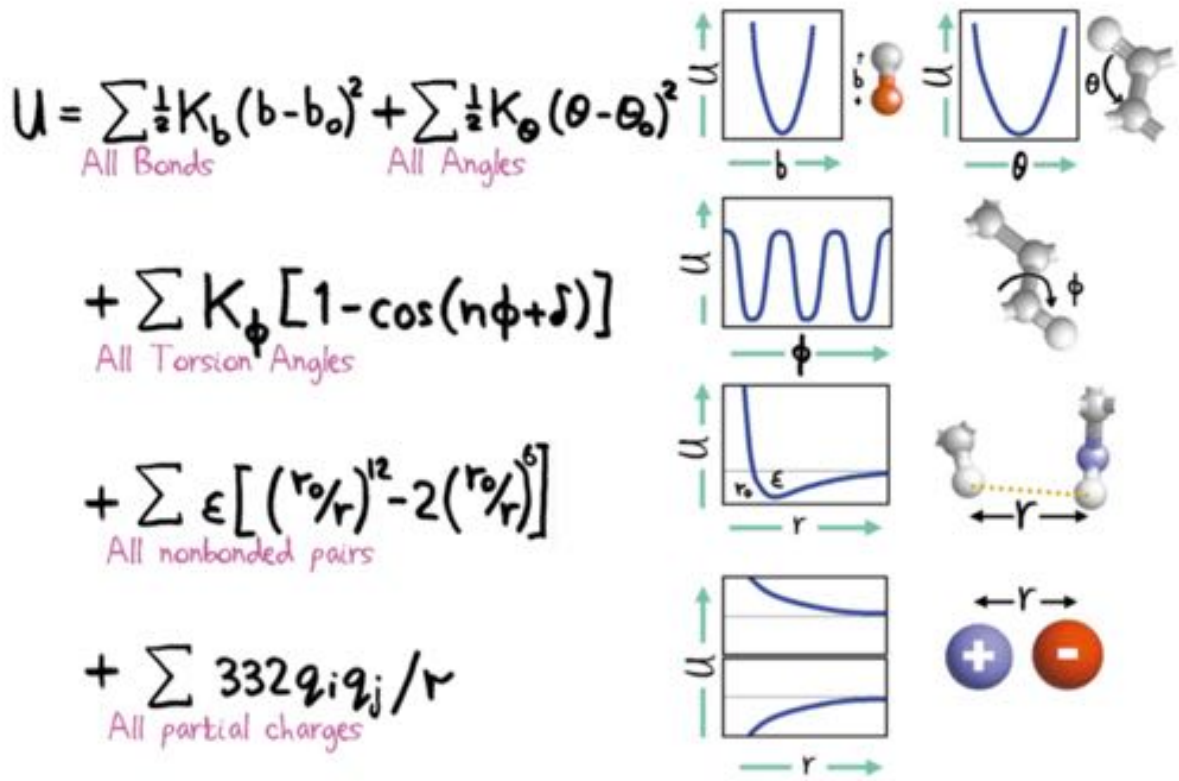
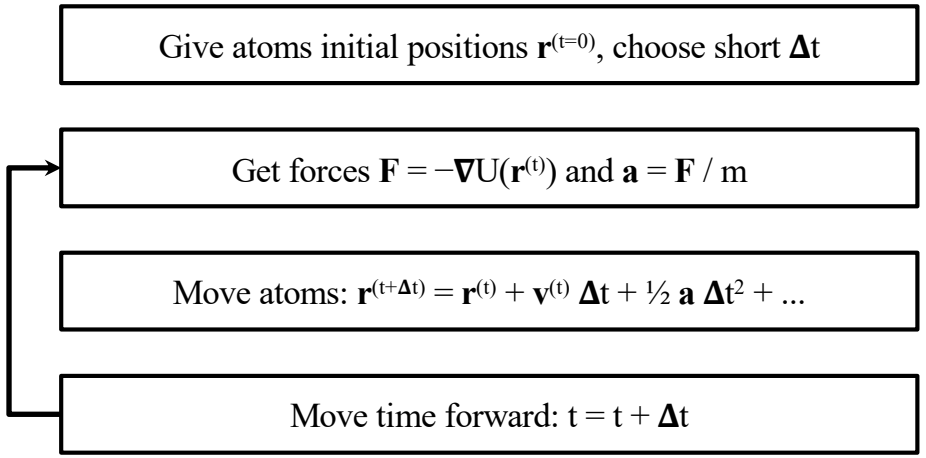
- There are different type of atomic interactions: **bonded** and **non-bonded**.
- **Energy functions** describe the different types of interactions.
- The **parameters** of the functions constitute a molecular **force-field** .



MD: Newtonian Time-propagation

- An MD simulation trajectory can be generated by iteratively applying an integration algorithm
- This algorithm is based on the Newton equations of motion
- Integration step in the order of magnitude of femtoseconds (1 fs = 1×10^{-15} s)
- Focus on the optimization of algorithms to do MD



Computer Aided Drug Discovery (CADD)

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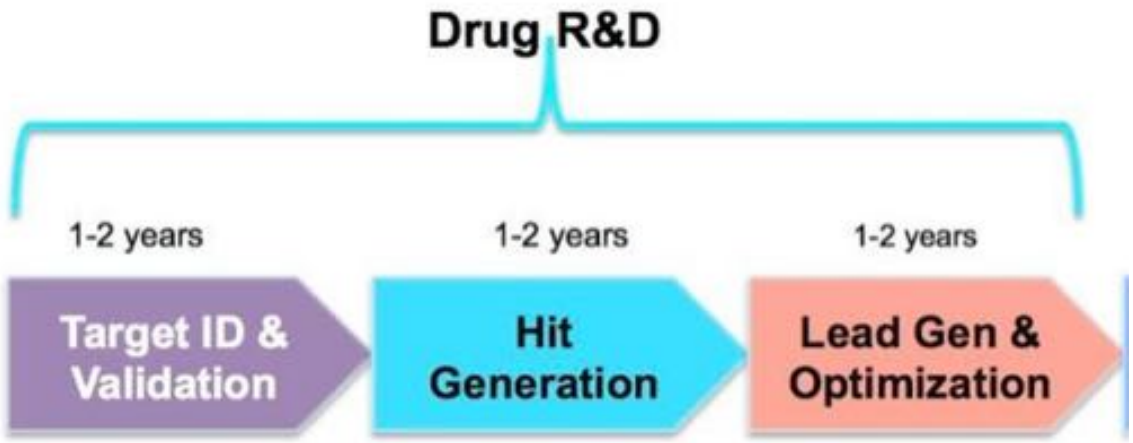
- The method of choice usually depends on a **speed / accuracy** trade-off.
- MD simulations provide a more **accurate solution**, while its computational cost keeps decreasing.



Comparative Modelling

Pocket detection
- MD simulations
- Knowledge-based prediction algorithms

Ligand generation
- QSAR
- Pharmacophore
- Library generation
- *De novo* design

Pose & affinity prediction
- Docking
- MD simulations

Lead Optimization
- QSAR
- Pharmacophores

***In silico* ADMET prediction**
- Knowledge-based prediction algorithms

Practical application

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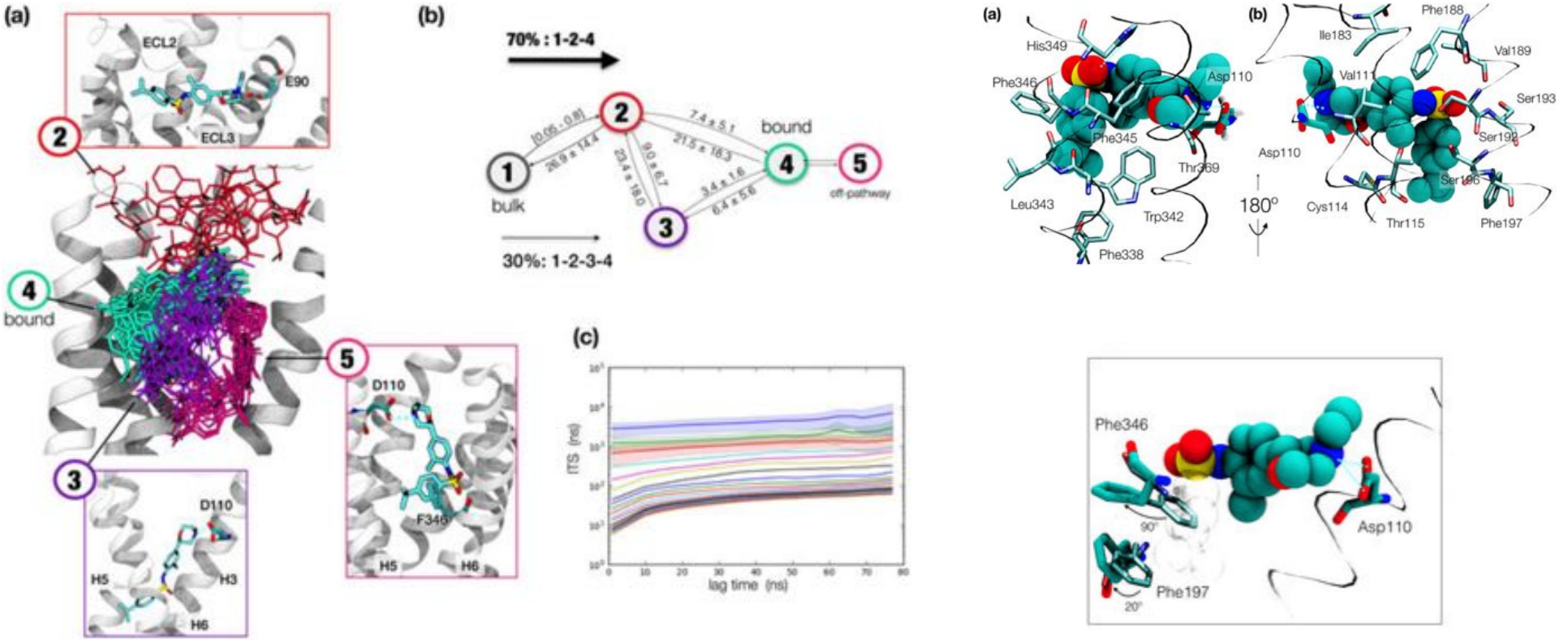
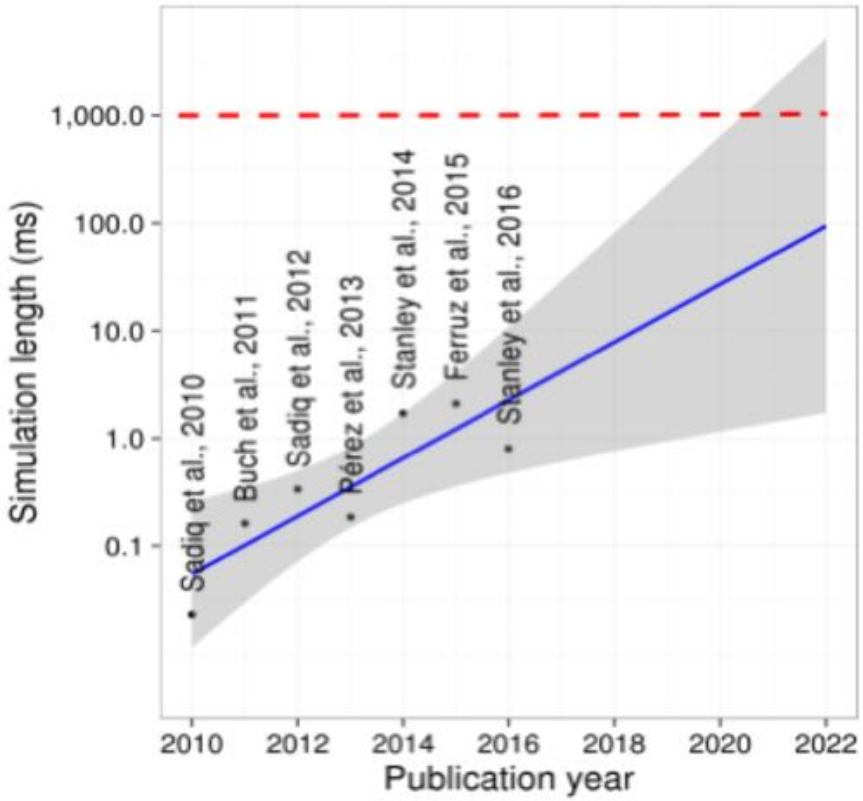
Cryptic pocket detection in Dopamine D3 receptor (GPCR)



Ferruz et al. (2017) Scientific Reports: doi:10.1038/s41598-018-19345-7

Decreasing computational cost of MD

- The first simulation of protein dynamics dates from 1977 and consisted of a **9.2 ps trajectory** of the bovine pancreatic trypsin inhibitor (BPTI) in vacuum.
- In 2010, a 1 ms trajectory of the same protein in explicit solvent was reported, which constitutes a 100 million increase in trajectory length compared to the first simulation



Decreasing computational cost of MD

- Implementation of MD codes for GPUs

ACEMD™ molecular simulations

- Distributed computing projects

- Development of special-purpose supercomputers (ANTON)

High-throughput MD

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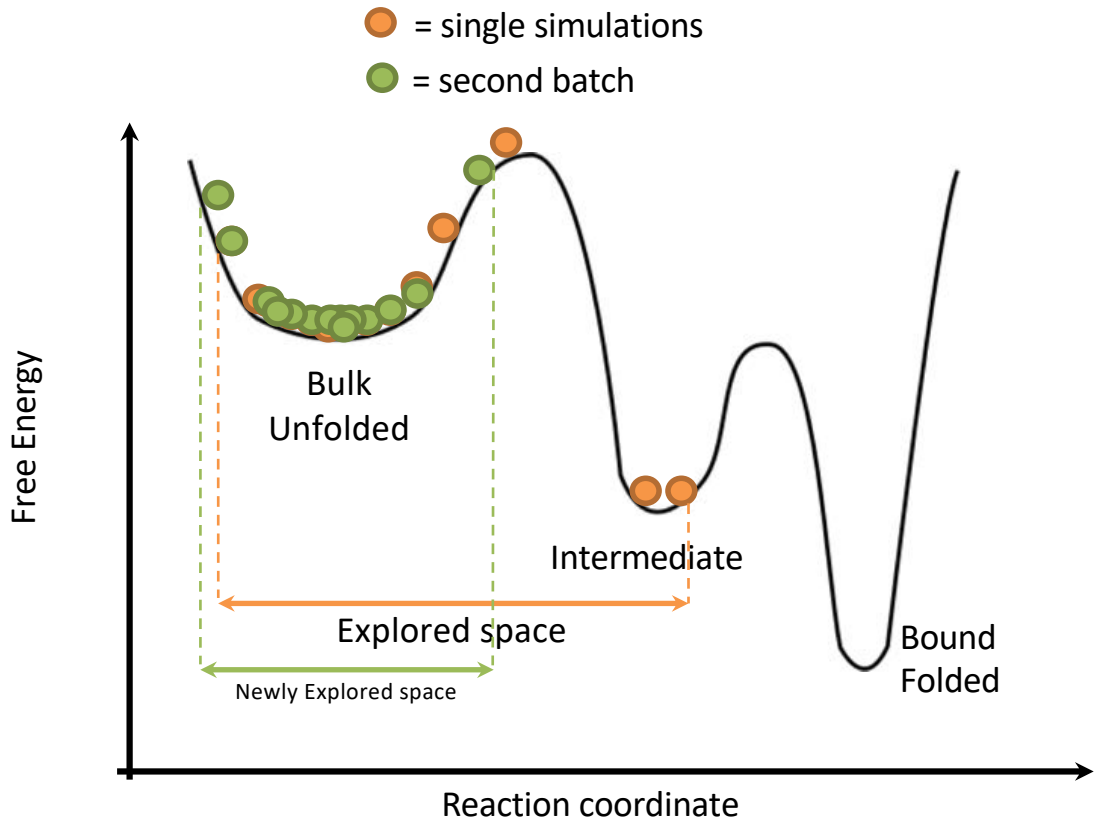
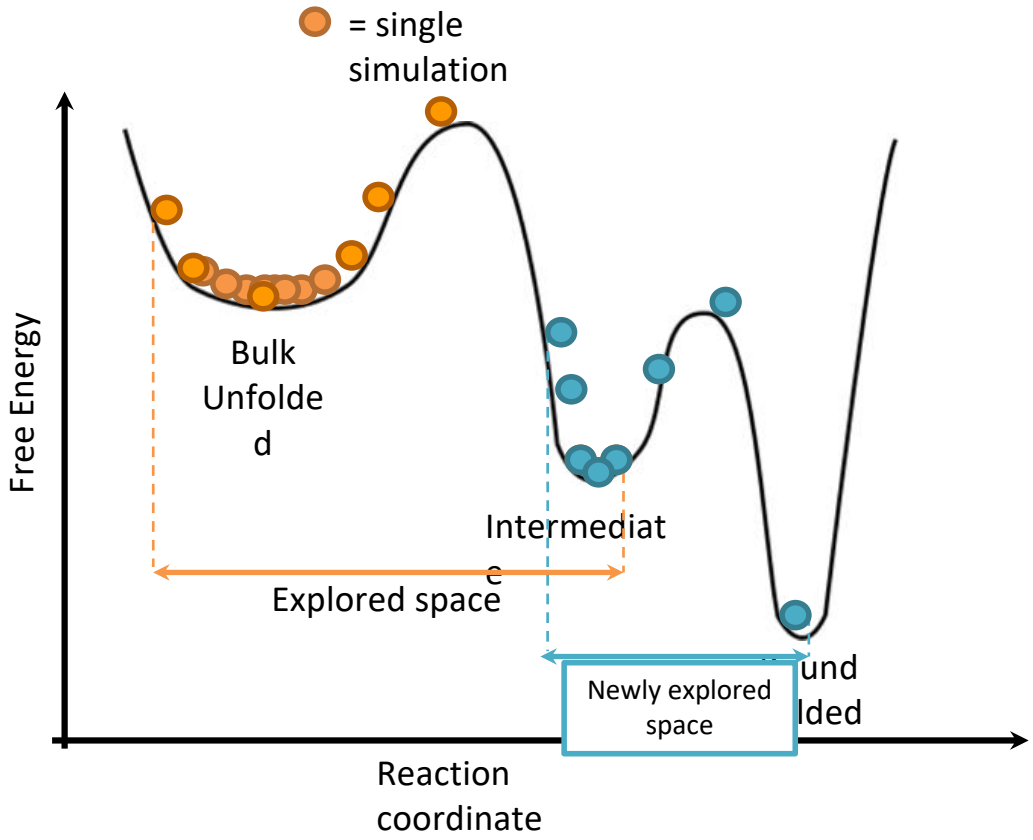
Naive Sampling



Adaptive Sampling



Adaptive Sampling

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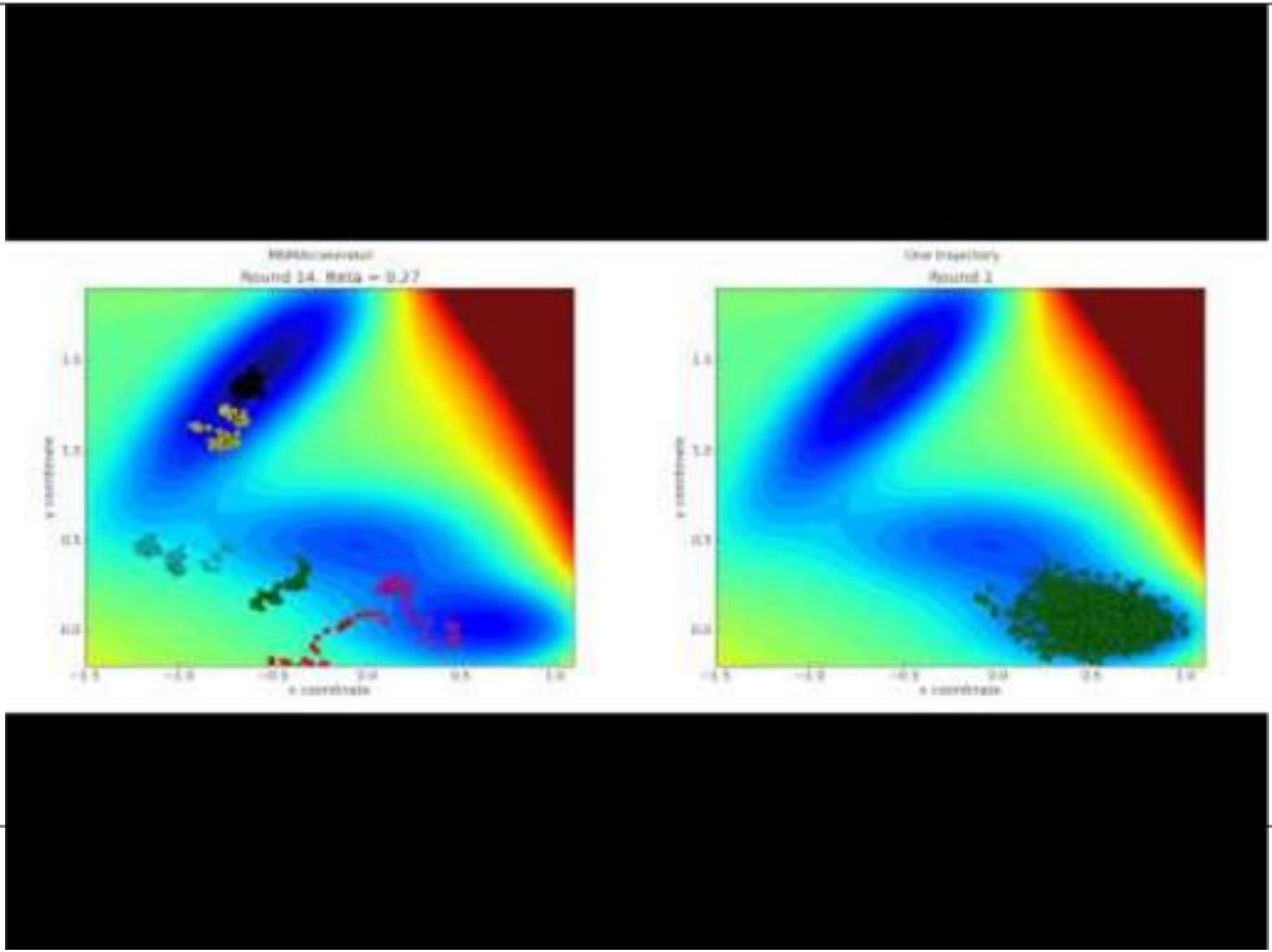

Markov State Models

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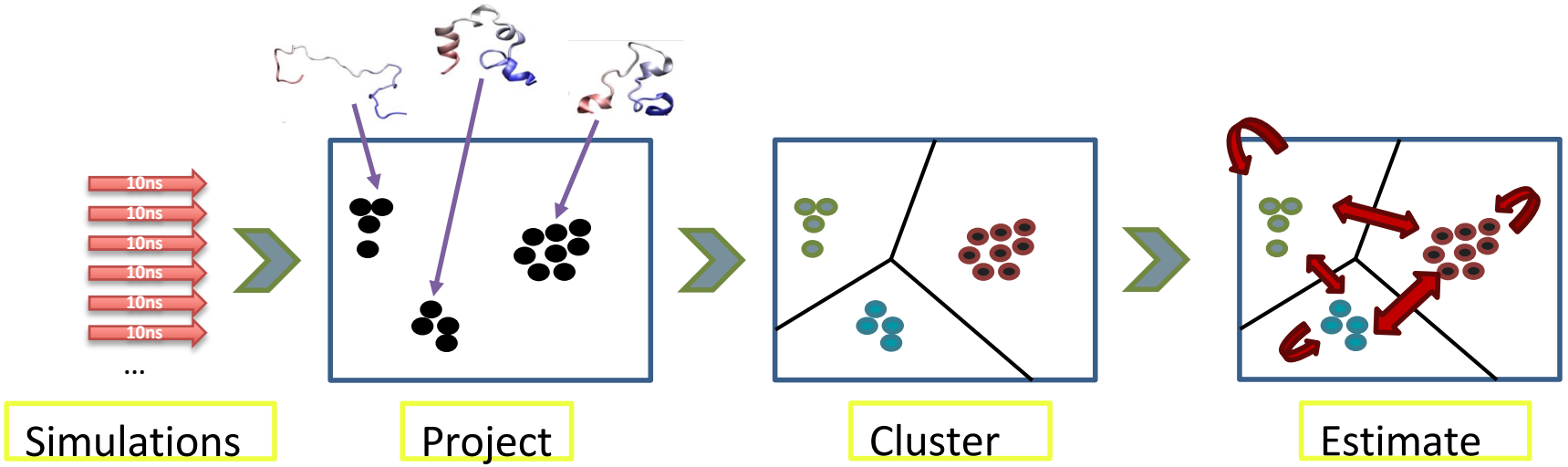
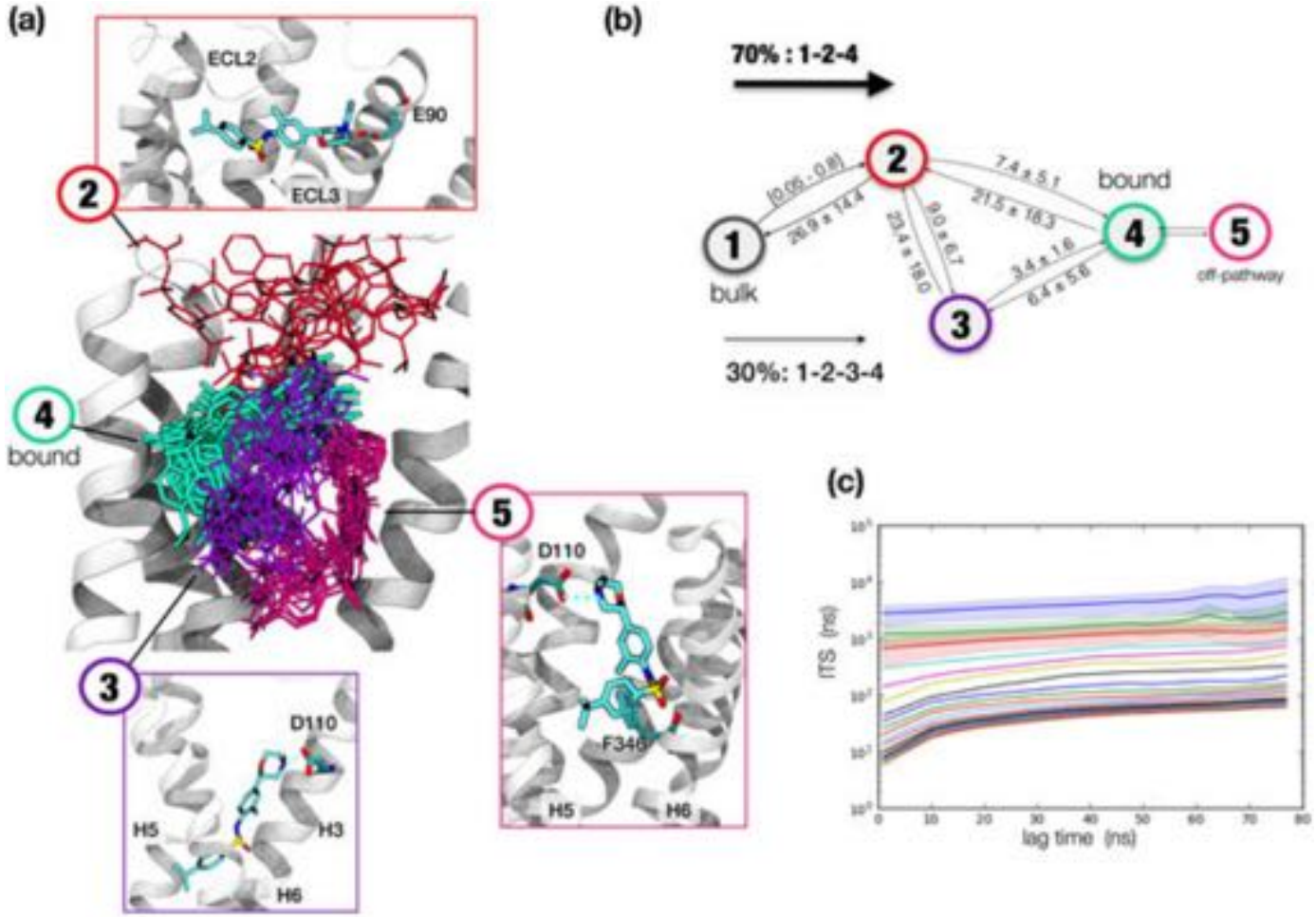


Markov State Models



Example case: Benzamidin-Trypsin

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HTMD

A python programmable environment for biomolecular discovery

System building	Simulation	Visualization	Analysis	Protocols
• Molecule manipulation • atomselection • **QM parametrize** • Solvate, Ionize • Build Charmm/Amber • **Protein Prep**	• **ACEMD** integrated, but HTMD is generic • Deployment locally, cluster, Amazon EC2 • Docking (vina) • Adaptive sampling • Standard sampling	• 3D viz integrated • webgl • VMD • Pathways	• Dimensionality reduction • Projections • Markov state models (pyEmma) • Affinities • Kinetics	• Equilibration protocols • Allosteric detection • Ligand binding • Conformation analysis • Pocket discovery • Protein placement • …

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Q&A

To pose a question, you can write your question
in the “Questions” tab

Thank you for participating!

…don't forget to fill in our feedback questionnaire…

Visit the CompBioMed website (www.compbiomed.eu/training)
for a full recording of this and other webinars,
to download the slides
and to keep updated on our upcoming trainings.
For any other question:
adria.perez@upf.edu

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