Workshop locale sul calcolo scientifico
4 Giugno 2015
Campus universitario, Parma

Sistemi computazionali per la ricerca farmaceutica e biomolecolare

Marco Mor

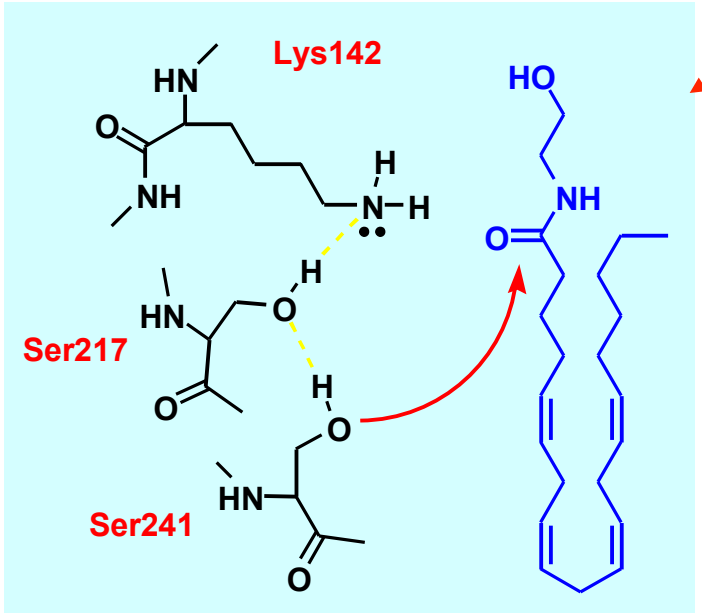
UNIVERSITÀ DEGLI STUDI DI PARMA
Diparimento di Farmacia

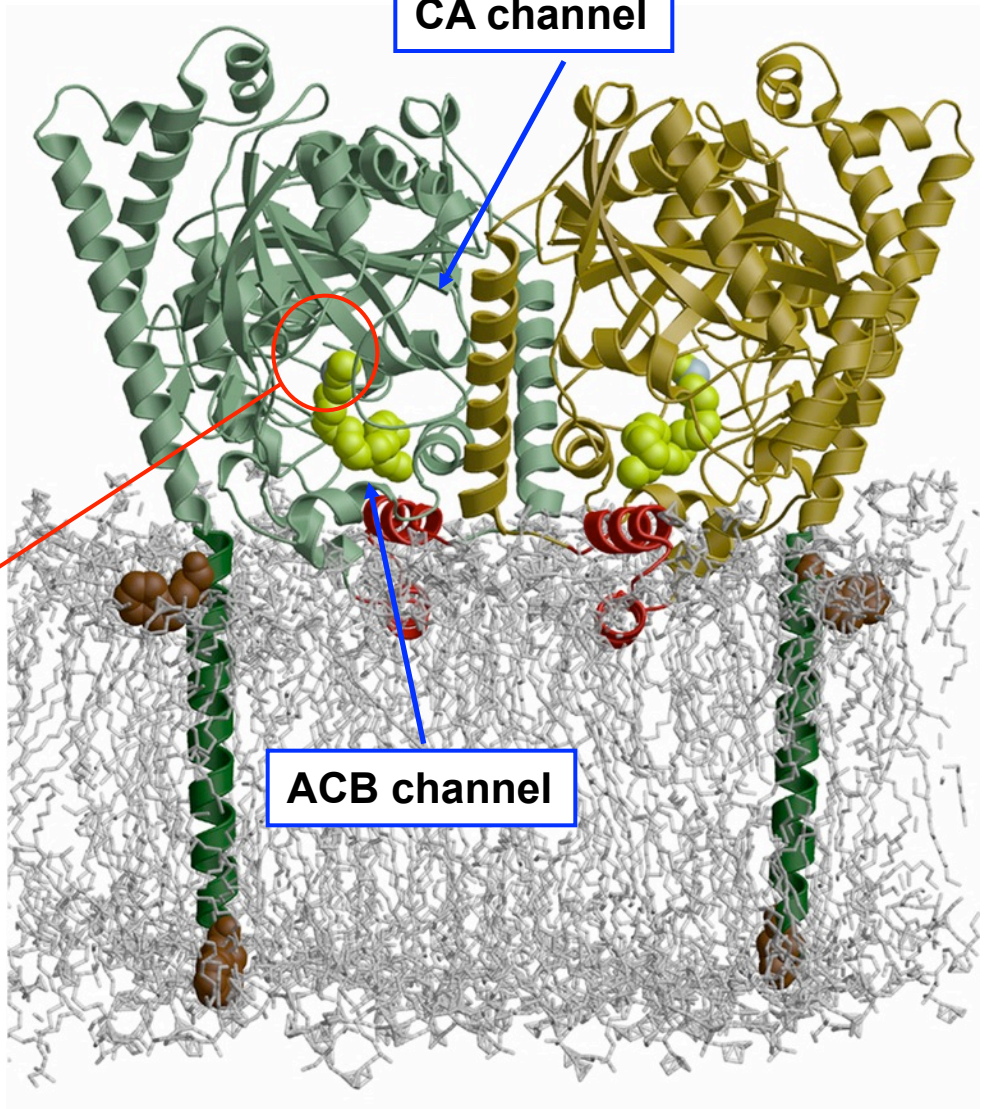
Sistemi computazionali per la ricerca farmaceutica e biomolecolare a Parma

- **- Dip. di Farmacia:**
  - Gabriele Costantino
  - Alessio Lodola
  - Marco Mor
  - Andrea Mozzarelli
  - Silvia Rivara
- **- Dip. di Sc. degli Alimenti**
  - Pietro Cozzini
- **- Dip di Fisica etc**
  - Eugenia Polverini
- **- Dip. di Bioscienze:**
  - Giorgio Dieci
  - Stefano Leonardi
  - Barbara Montanini
  - Simone Ottonello
  - Riccaro Percudani
  - Claudio Rivetti
  - Marco Ventura
  - Massimiliano Zaniboni

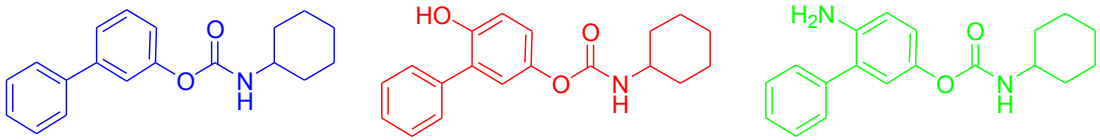
Fatty-Acid Amide Hydrolase

- **Hydrolysis of NAE**
  - AEA: endocannabinoid
  - PEA: antiinflammatory
- **Inhibitors**
  - Pain, inflammation, nicotine/ cocaine abuse
- **Uncommon catalytic triad**

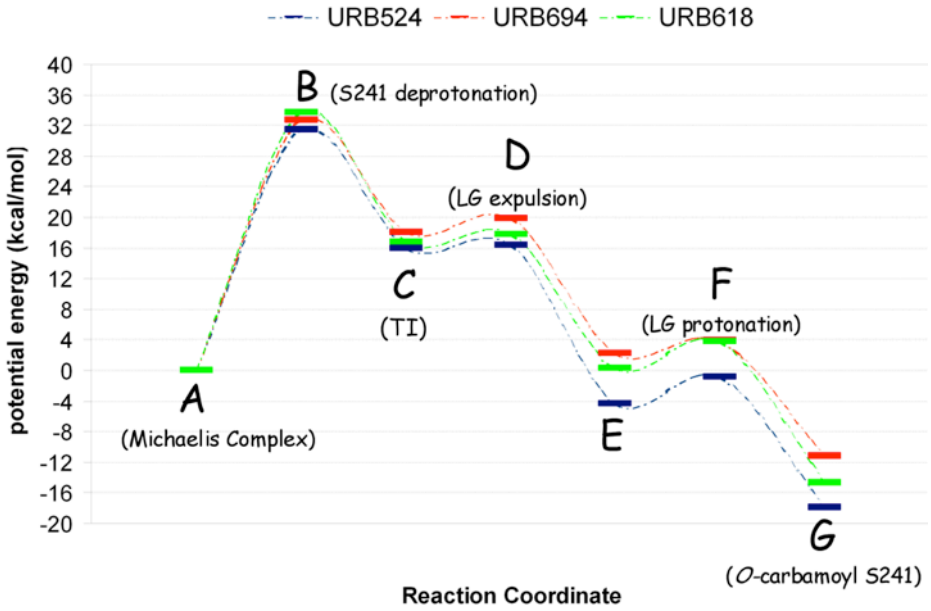


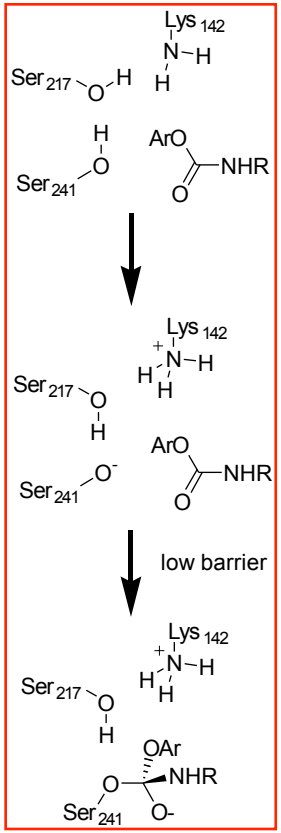


Mechanism of FAAH inhibitors



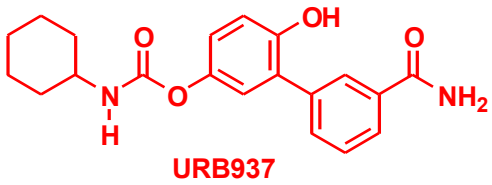
QM/MM potential energies:





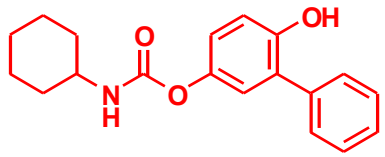
- **It is possible to modulate chemical/biological stability while conserving FAAH inhibition**

Lodola A, *et al.Chem Commun 47* (2011) 2517



Clapper JR, Moreno-Sanz G, Russo R, Guijarro A, Vacondio F, Duranti A, Tontini A, Sanchini S, Sciolino NR, Spradley JM, Hohmann AG, Calignano A, Mor M, Tarzia G, Piomelli D.
Nature Neuroscience 13 (2010), 1265

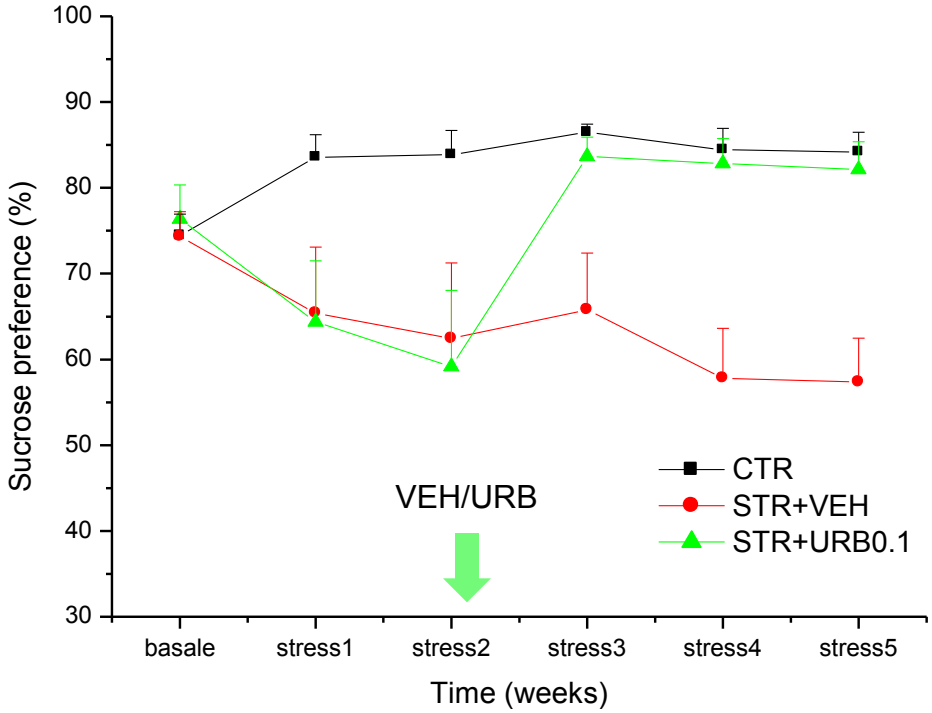
Second-generation URB: effect on stress-induced depression

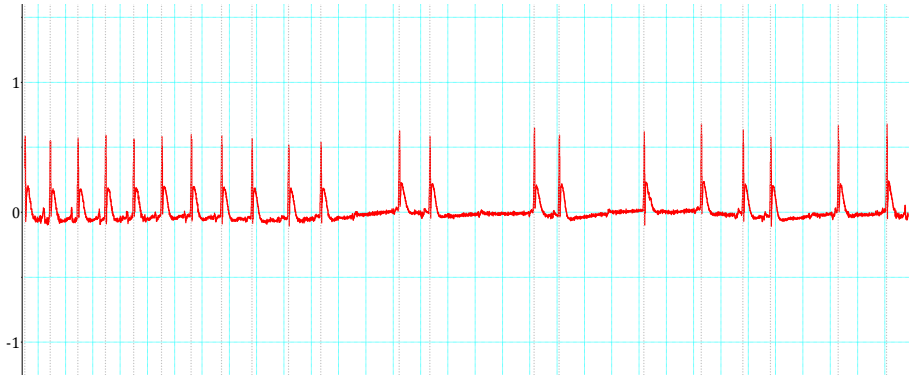


URB694

- At **0.1 mg/kg/die** resolves anhedonia in a translational model of social stress

- Cardiac arrhythmias in Vehicle-, but not URB694-treated rats

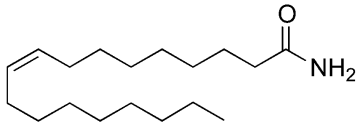




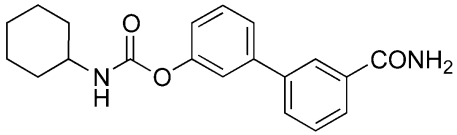
Carnevali L *et al. submitted*

Inhibitor reversibility: QM/MM energy profiles for deacylation

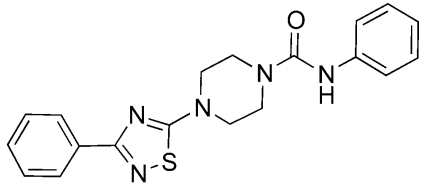
- **QM / MM**



oleamide, (**1**)

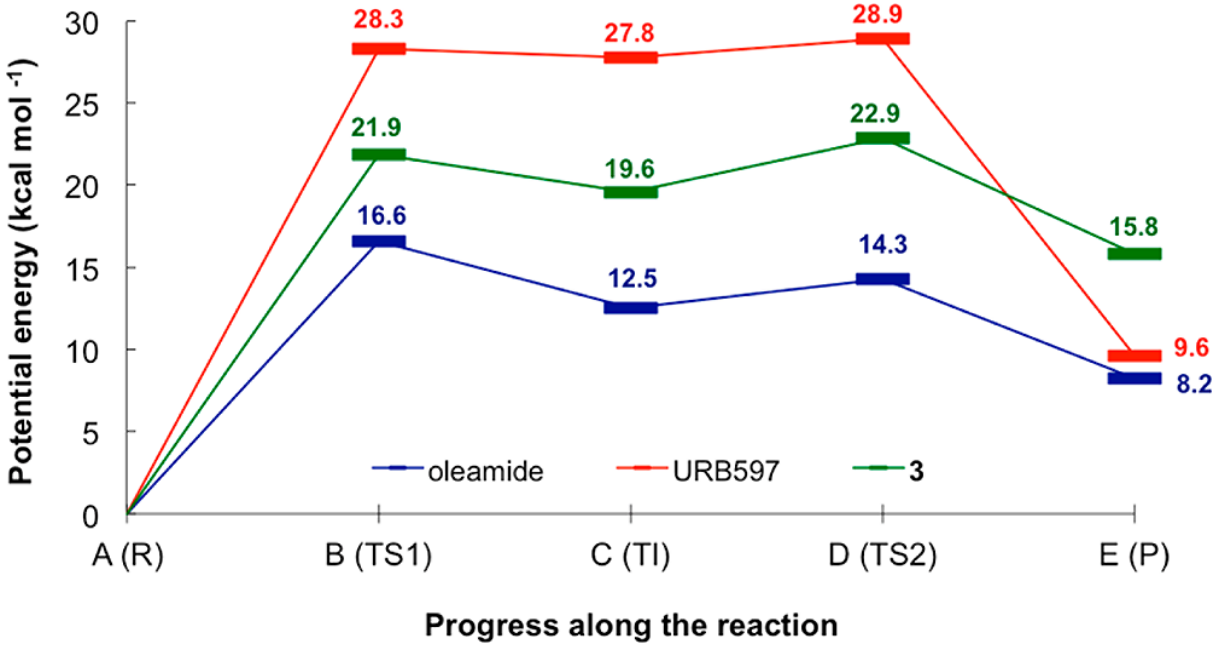


URB597, (**2**)



JNJ1661010, (**3**)

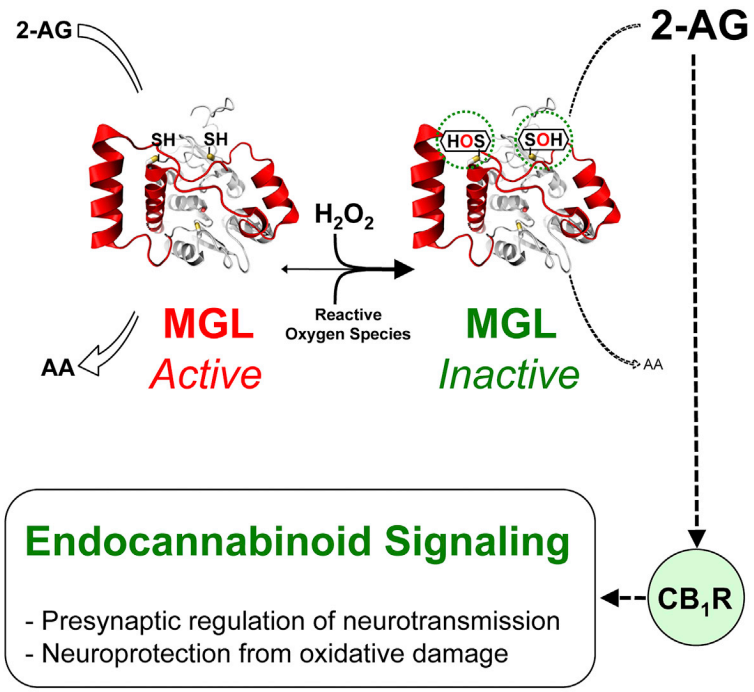
R: Reactant (adduct)
TS: Transition State
TI: Tetrahedral Intermediate
P: Products

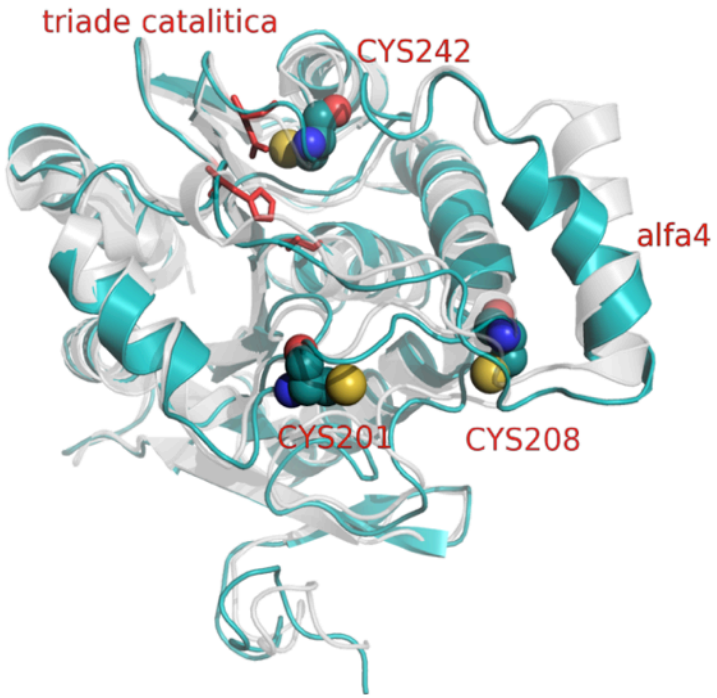


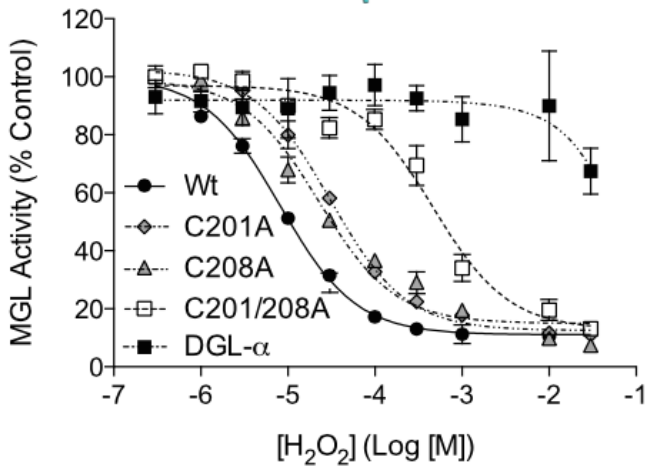
- It is possible to modulate the rate of enzyme regeneration

Lodola A., Capoferri L, Rivara S., Tarzia G., Piomelli D. Mulholland AJ, Mor M, *J Med Chem. 56,* (2013) 2500

MGL: the other endocannabinoid watchdog



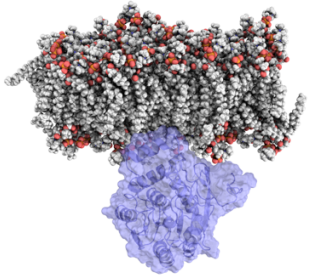


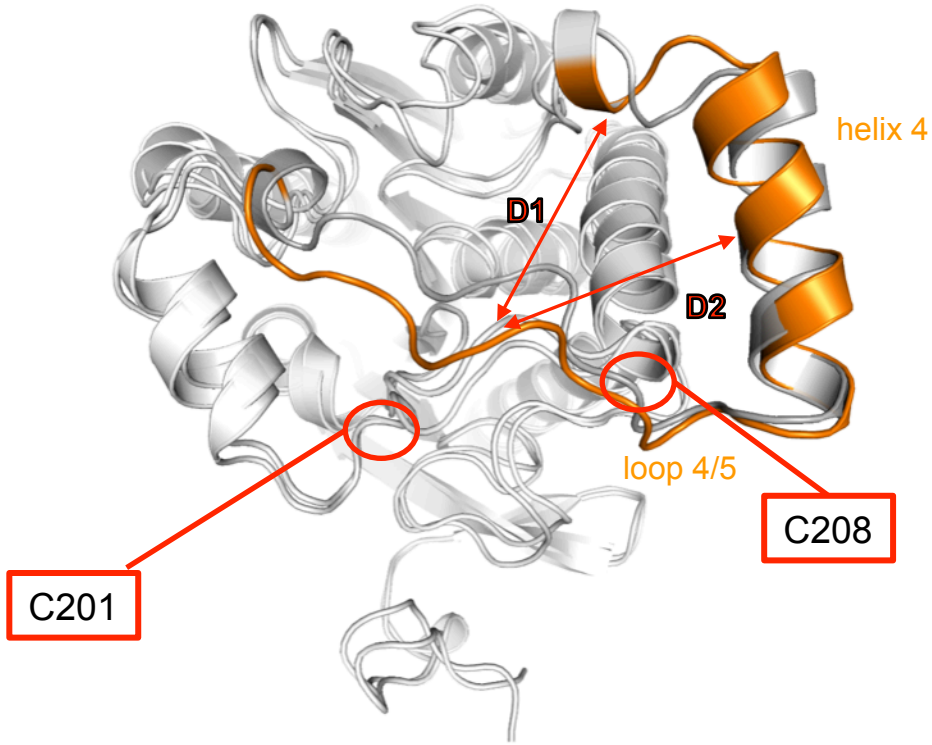


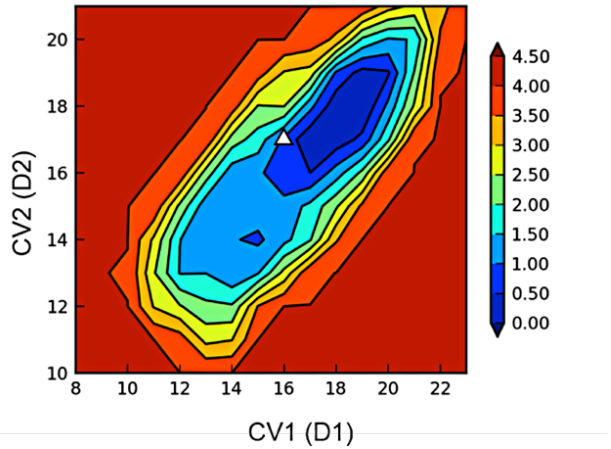
Dotsey EY *et al. Chem Biol 22(2015),* 619

Cysteine binding affects substrate recruitment

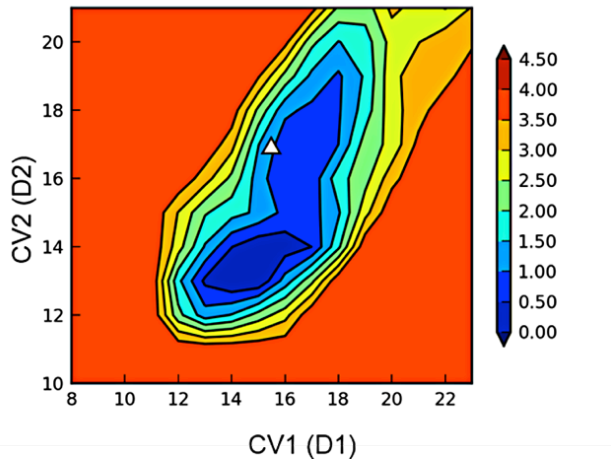
- **MD / Metadynamics simulations**
  - the lid domain can assume open and closed conformations
  - conformational equilibrium depends on
    - membrane
    - Modification of C201 and/or C208







C201-SOH

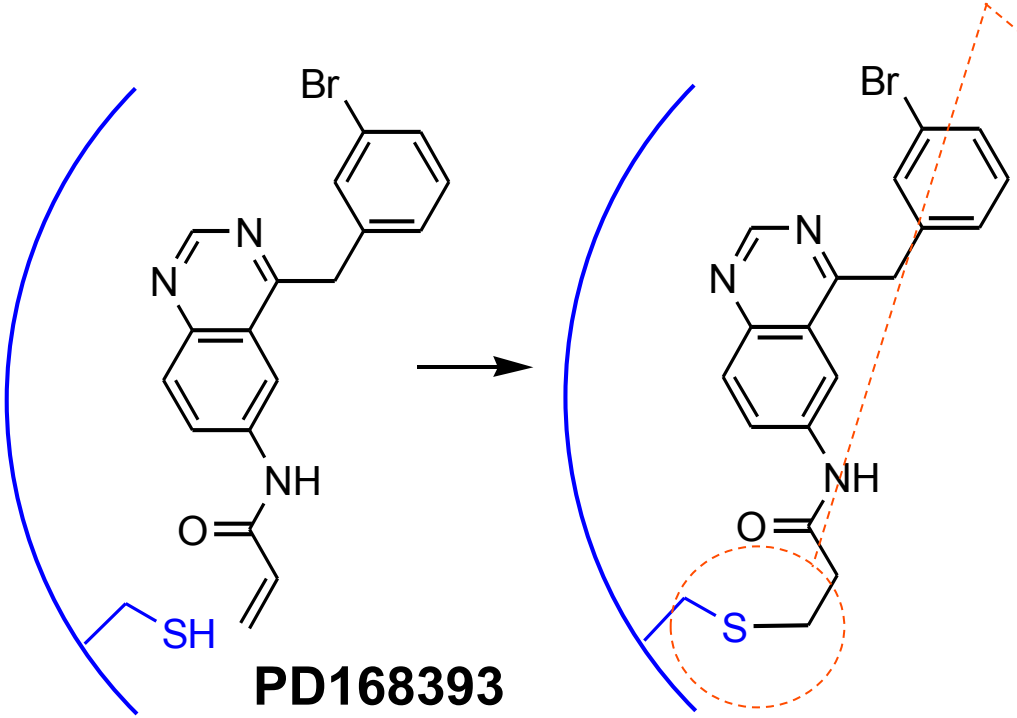


Scalvini L *et al manuscript in preparation*

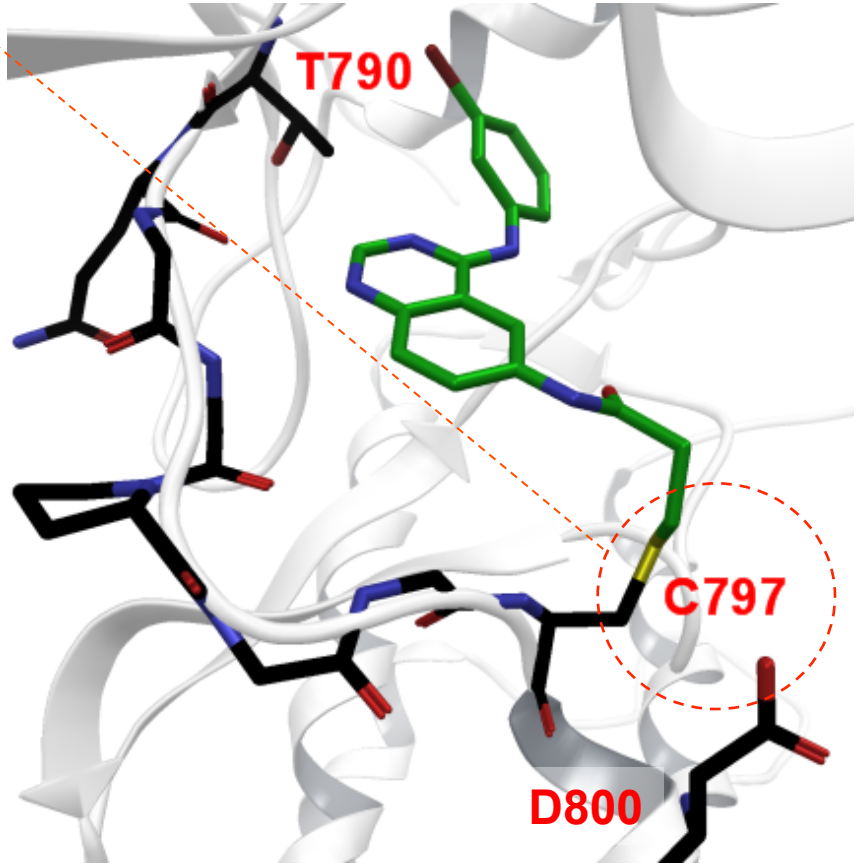
Irreversible EGFR inhibitors: alkylation mechanism

- **Irreversible inhibitors of EGFR overcome tumor resistance**

Alkylation of Cys^{797}

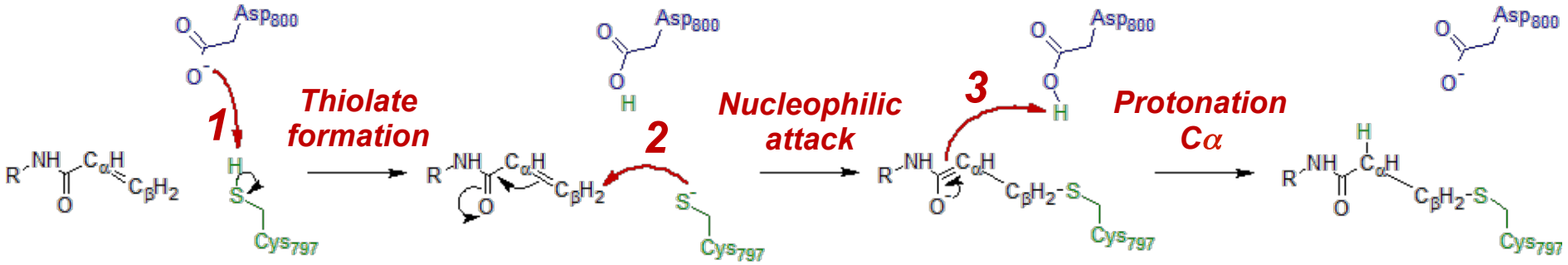


PD168393



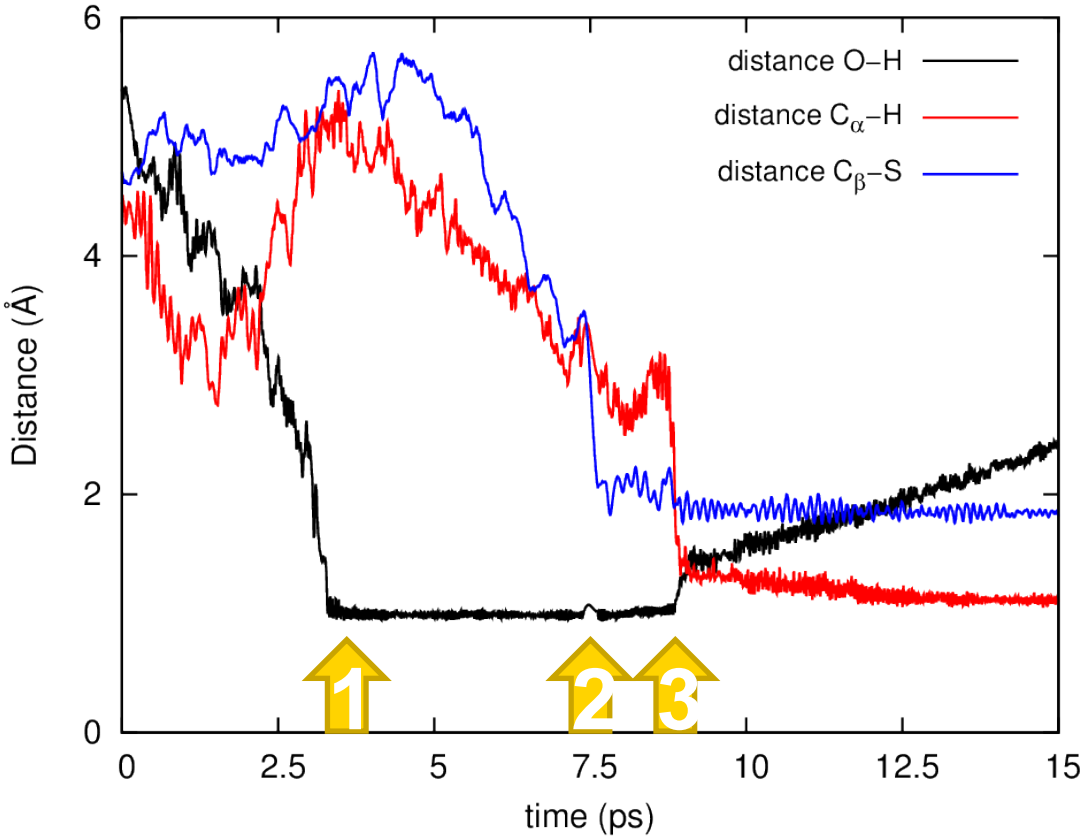
EGFR-TK domain co-crystallized with PD168393

QM/MM reaction modeling by path-collective variables



- **SCC-DFTB/AMBER99SB**
- **Steered-MD (SMD)**
  - path finding and refinement
- **Guess path**
  - stepwise simulation through 3 distance variables
- **Umbrella Sampling (US)**
  - PMF calculation

- **Asp_{800} is a key residue for nucleophilic activation**



Gruppo di chimica farmaceutica – Mor-Rivara-Lodola

- **Applicazioni e modelli**
  - Meccanismi di farmaci (“covalenti”, allosterici)
    - QM/MM, MD, FE-paths, MD, Enhanced sampling
  - Virtual screening / SAR analysis
    - Comparative modelling, Docking/scoring, FEP, Modelli farmacoforici
  - Modelli statistici di relazioni-struttura attività
- **Software di modellistica molecolare**
  - Preferenzialmente Schroedinger
- **Risorse impiegate**
  - Multi-core CPU: 6-8 PC biprocessore (Xeon 8-core)
  - GPU: 8 GPU (Gtx 780) in 4-6 PC
    - 50000 atomi: 20-50 ns/die/GPU
  - Risorse esterne in collaborazione (sporadiche)
- **Necessità**
  - Corrente stabile, ambienti refrigerati
  - Data storage
  - Sistemi per calcolo parallelo
  - GPU

HPC-based Approaches in Med Chem.

P.I Gabriele Costantino

P4T

- Optimization of docking software performances:

  large docking runs to fine-tune software parameters with following test cases:

  - 100-500 proteins and 1 ligand
  - around 100 proteins a compounds library > 100 000 small molecules

  → Several parallel indipendent jobs + statistical analysis of results (matlab/R)
  → Resources:
  CINECA computational resources (previously PLX and EURORA, now GALILEO) : 1Mio core hours

- Hit/Lead discovery:

  docking runs and VS for specific target of interest + computation of DMPK properties + pharmacophore models etc…
  → Internal resources (PC workstations 16 core)

- Target fishing/ drug repositioning :

  docking runs and VS using an in-house protein library
  → Internal resources (PC workstations 8 core) & CINECA (150 000 core hours)

- Enhanced Sampling Techniques (MD, SMD, metaMD):
  - Sampling of conformational space of biomolecules, reconstraction of binding and unbinding

  → Internal resources (PC workstations 8 core) & CINECA (150 000 core hours)

COMPUTATIONAL FOOD CHEMISTRY

Pietro Cozzini - Dipartimento di Scienze degli Alimenti

Stato dell'arte:
Virtual Screening, Docking/Scoring su sistemi locali
Dinamica Molecolare su sistemi CINECA e Universita' di Modena
Dinamica Molecolare e sviluppo di scoring functions su "Mare Nostrum" a Barcellona
Sviluppo di software per simulazioni ab initio su sistemi multiprocessore New Mexico University e Virginia Commonwealth University

Desiderata:
Possibilita' di sistemi 3D per la visualizzazione e per la prototipazione/stampa

University of Parma
Dept. of Food Science
Molecular Modelling Laboratory

University of Parma
Department of Food Science
Food for thoughts

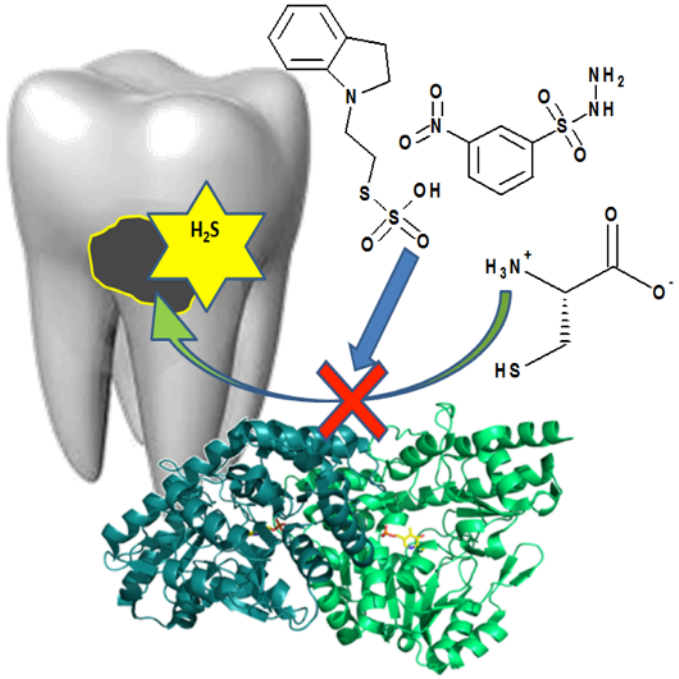
CHEMMEDCHEM
FULL PAPERS

ChemPubSoc Europe

DOI: 10.1002/cmdc.201300527

Targeting Cystalysin, a Virulence Factor of *Treponema denticola*-Supported Periodontitis

Francesca Spyrakis,[d, e] Barbara Cellini,*[a] Stefano Bruno,[b] Paolo Benedetti,[f] Emanuele Carosati,[g] Gabriele Cruciani,[g] Fabrizio Micheli,[h] Antonio Felici,[h] Pietro Cozzini,[c, d] Glen E. Kellogg,[i] Carla Borri Voltattorni,[a] and Andrea Mozzarelli*[b, c]

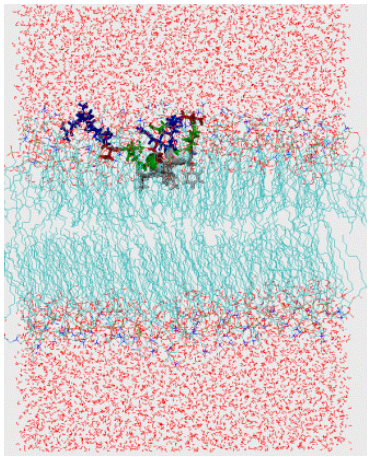


Prof. Eugenia Polverini
Dipartimento di Fisica e Scienze della Terra - Sezione di Biofisica
Università di Parma

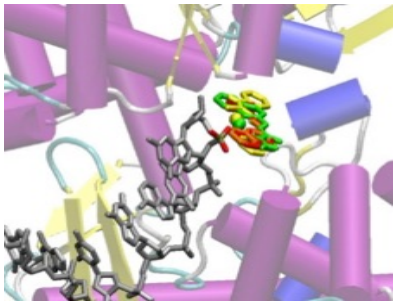
Struttura e dinamica di biomolecole in relazione alla loro funzione
Tecniche computazionali per la simulazione di sistemi proteici:
Dinamica Molecolare
Docking Molecolare
Modeling Molecolare

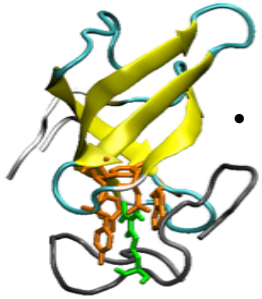
- interazione proteina-membrana:
- Proteina Basica della Mielina in doppio strato lipidico

→ rilevanza nella **sclerosi multipla**



- disegno di inibitori di enzimi del ciclo cellulare, a scopo **antitumorale**





- interazione della proteina SMN col sistema spliceosomale

→ rilevanza nella **atrofia muscolare spinale**

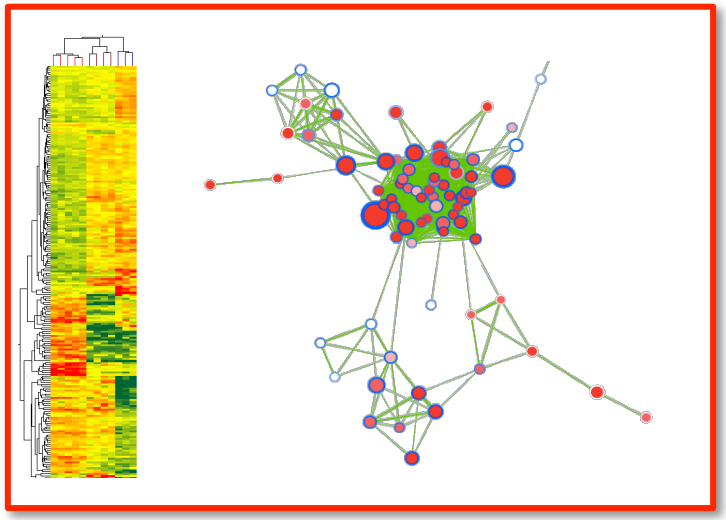
Risorse utilizzate: Cluster per il calcolo numerico intensivo del Dipartimento di Fisica.
Facility canadese di High Performance Computing SHARCNET (Shared Hierarchical Academic Research Computing Network: www.sharcnet.ca), Compute/Calcul Canada (solo relativamente al progetto mielina).

Software di calcolo intensivo principalmente utilizzati: Gromacs (parallelo) per simulazioni di dinamica molecolare. Autodock4 (seriale) per simulazioni di docking.

Necessità: ampliamento della potenza di calcolo, in particolare per calcolo parallelo; risorse GPU

BARBARA MONTANINI, SIMONE OTTONELLO

Dipartimento di Bioscienze



PROGETTO IN CORSO

Strategie terapeutiche innovative basate sull'identificazione di nuovi composti antivirali:

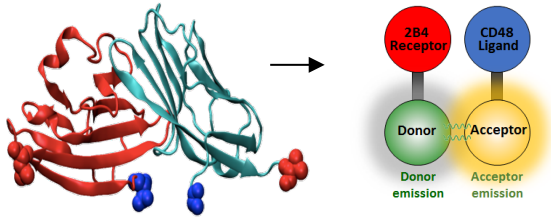
1- Identificazione di target molecolari per il recupero dell'exhaustion in pazienti con infezione cronica da epatite B e C

- Gene expression analysis *

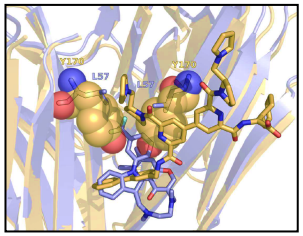
- Network analysis

2- Identificazione di molecole in grado di bloccare interazioni inibitorie recettore-ligando, responsabili dell'exhaustion.

- **Screening di piccole molecole mediante tecnologia BRET in lievito**
- **Virtual screening and hit-to-lead optimization.****



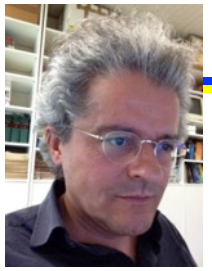
Interaction reproduced in BRET



Interaction inhibitor

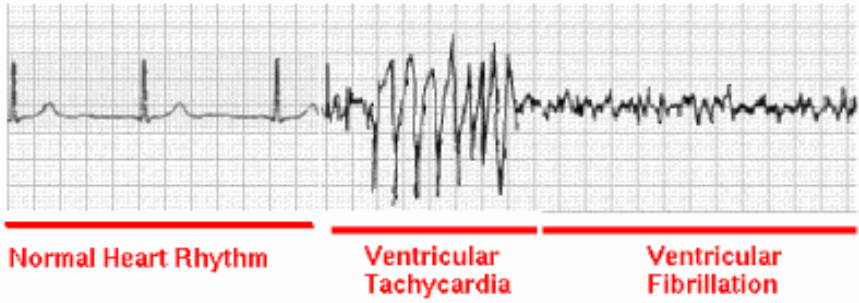
IN COLLABORAZIONE CON:

- U.O. di Malattie Infettive ed Epatologia, Azienda Ospedaliero-Universitaria di Parma *
- Dipartimento di Farmacia**



MASSIMILIANO ZANIBONI

Dipartimento di Bioscienze

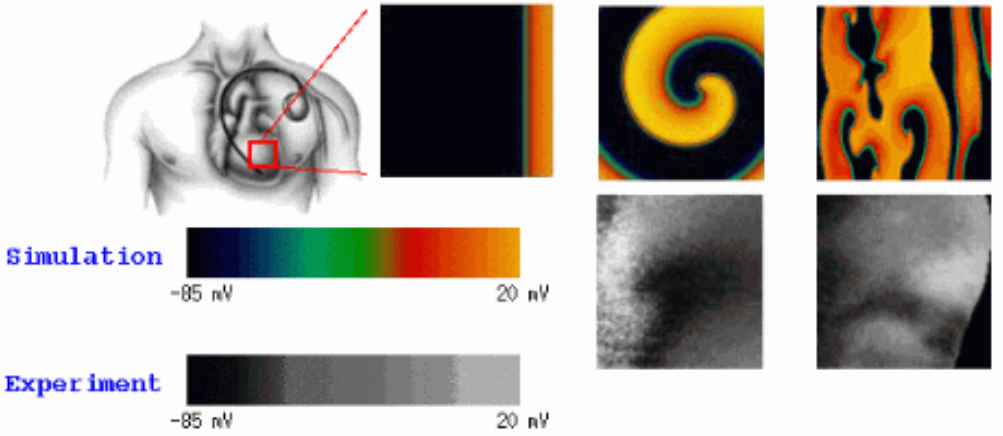


INTERESSI DI RICERCA

Studio ***in vivo*** e ***in silico*** della eccitabilità cellulare cardiaca

APPLICAZIONI

1. Modulazione farmacologica pacemaking cardiaco
2. Controllo transizione fisio-patologica del ritmo



COLLABORAZIONI RECENTI

CHIESI Farmaceutici S.p.A.

NEH Cardiovascular Research and Training Institute
University of Utah, USA.

1. **Modelli tipo Hodgkin-Huxley** della eccitabilità elettrica cellulare cardiaca (POTENZIALE D'AZIONE)
   Sistemi ODE risolti numericamente in contesti - zero-dim.(***cellula singola***)
   - mono-dim. (***cavo***)
   - bi- e tri-dim. (***tessuto***)

2. **Risorse hardware utilizzate ad oggi:** - PC Intel Core, CPU 2,50 GHz, RAM 4.00 GB, 64 bit op. sys.
   - Macchina virtuale (grid-ui 2) Vmware SL5 User Interface (**FISICA**)
   - Macchina multi-core SIRIO (complessivi 128 GB RAM) (**CCE**)

3. **DESIDERATA:** migliorare efficienza simulazioni ottimizzando interazione competenze (RICERCA-CALCOLO)

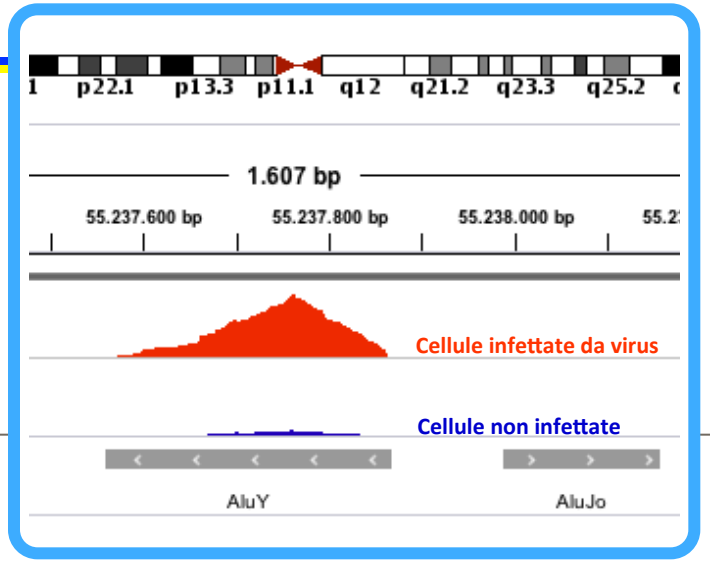
GIORGIO DIECI

Dipartimento di Bioscienze

Collaboratore interno per approcci computazionali:
DAVIDE CARNEVALI

INTERESSI DI RICERCA

Genomica, epigenomica e trascrittomica



APPLICAZIONI

Analisi di dati Next Generation Sequencing
(RNA-Seq, ChIP-Seq, Methyl-Seq).
Allineamento reads, assemblaggio del trascrittoma, assemblaggio del genoma, analisi statistiche
(Programmi: Bowtie, TopHat, STAR, Cufflinks, Scripture, Velvet, ABySS, R/Bioconductor, Matlab etc)

MODELLI COMPUTAZIONALI

Metodo "Burrows-Wheeler transform (BWT)-based" per allineamento di reads al genoma, De Bruijn graph per assemblaggio del genoma e ricostruzione del trascrittoma

RISORSE HARDWARE UTILIZZATE

Macchina multi-core SIRIO (COMPLESSIVI 128 GB RAM, 24 CPU, in condivisione)
NAS (Network Attached Storage) per spazio disco supplementare

DESIDERATA

Cluster che permetta sia di distribuire i processi computazionali parallelizzati, sia di eseguire programmi a processore singolo con molta RAM (>32GB).
Lo spazio disco richiesto durante le fasi di elaborazione varia da 500 Gb a 2/3 Tb. Lo spazio disco richiesto per archiviazione si può inizialmente stimare in 4/6 Tb, ma tenderà a crescere in futuro.

Laboratorio di Biochimica, Biologia Molecolare e Bioinformatica

R. Percudani

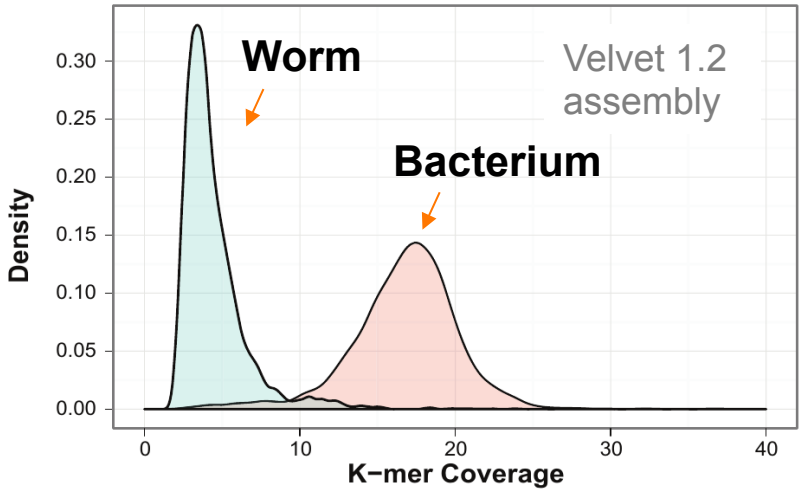
Genome data mininig

Worm-Bacterium genome assembly
sirio.unipr.it (128 Gb RAM; 500 Gb HD)

- Reads len: 76 bp
- Reads num.: 150 M
- Genome size: 0.1 G
- RAM: 40 Gb
- Storage: 100 Gb

Primate genome assembly

- Reads len: 50 bp
- Reads num.: 500 M
- Genome size: 3 G
- RAM (ext.): 350 Gb
- Storage (ext.): 500 Gb



A Microbial Metagenome (*Leucobacter* sp.) in *Caenorhabditis* Whole Genome Sequences

Riccardo Percudani

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