Can nuclear theory help find an anti-viral drug for COVID-19?

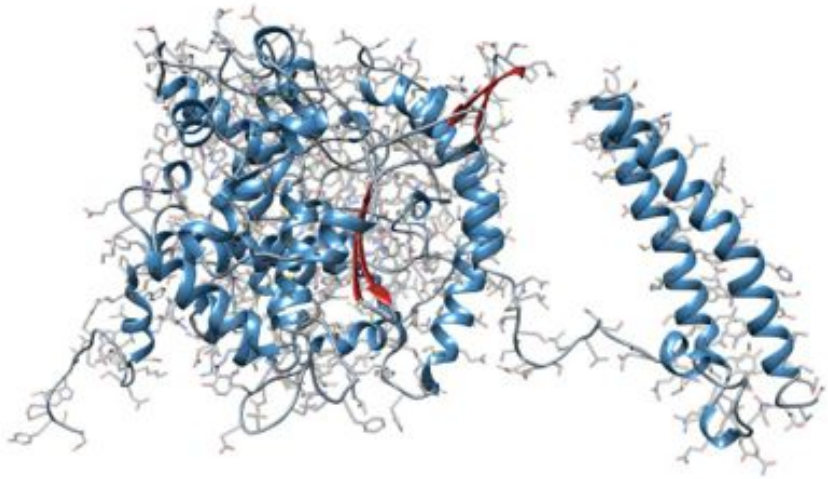
Pietro Faccioli

UNIVERSITÀ DEGLI STUDI DI TRENTO

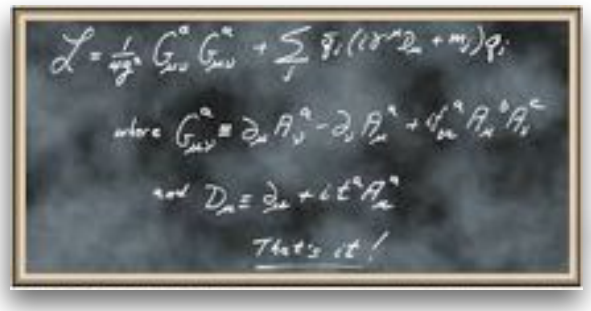
Dipartimento di Fisica

TIFPA

Trento Institute for Fundamental Physics and Applications

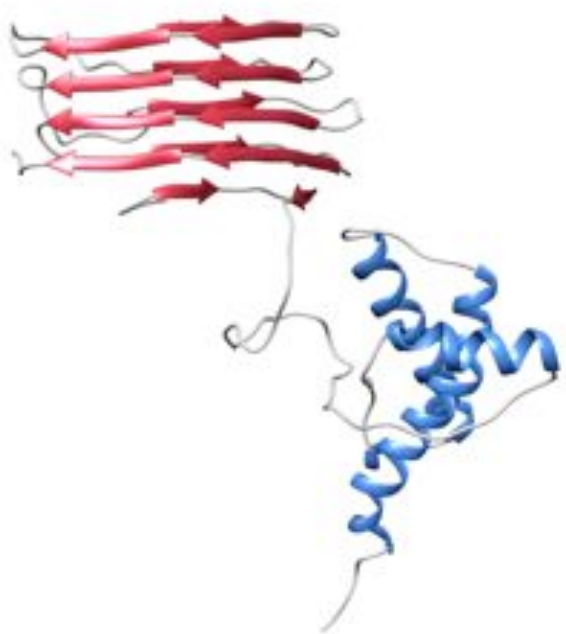


A LONG JOURNEY



??????

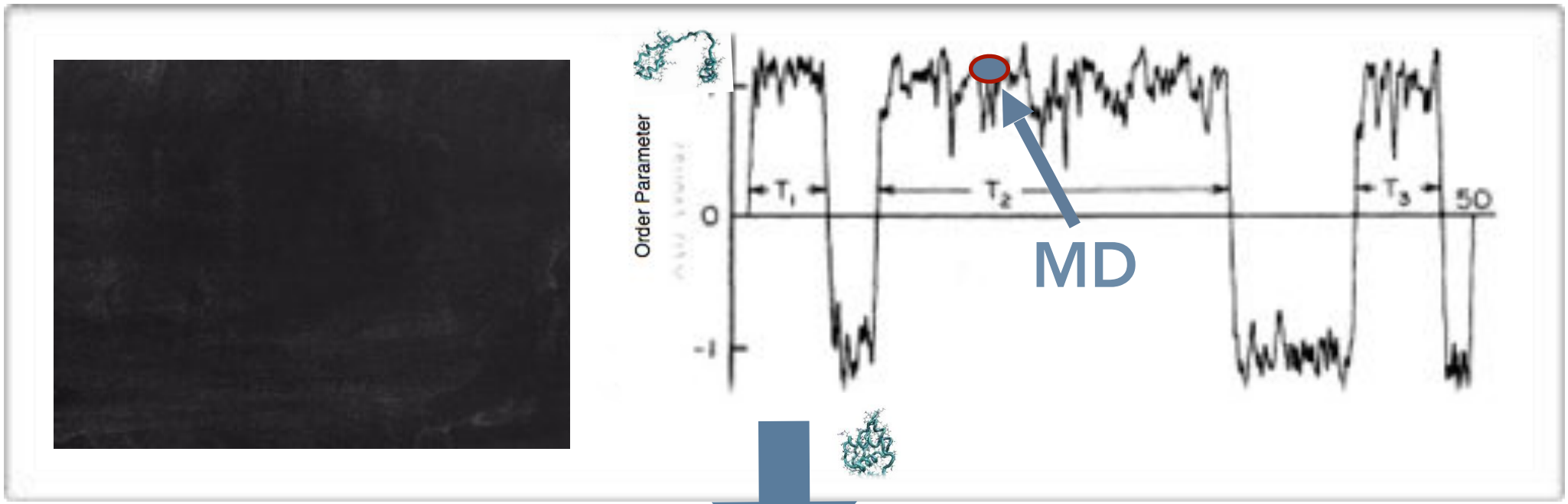
REDUCTIONIST'S APPROACH TO MOLECULAR BIOLOGY

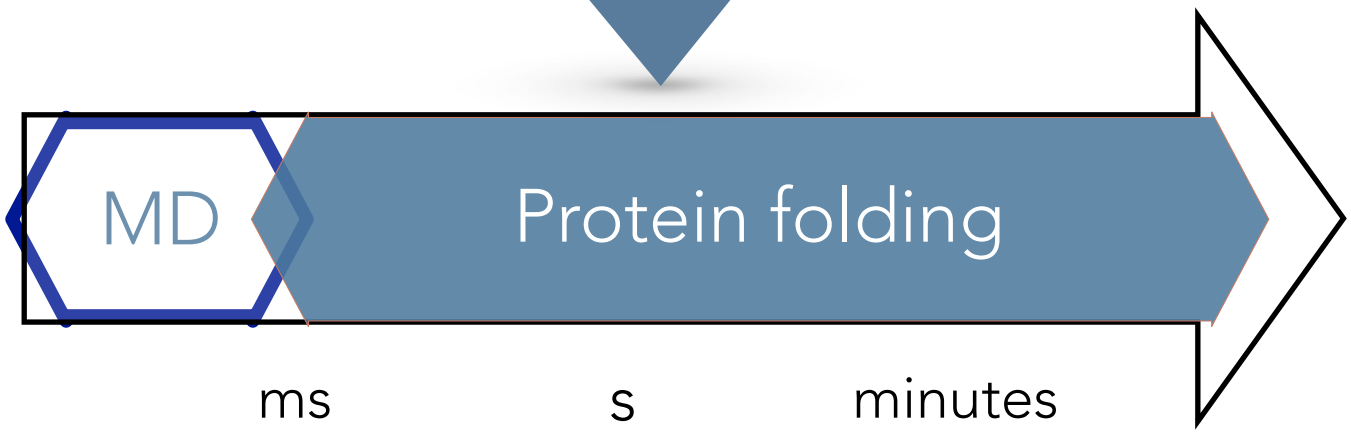


Challenge:

Integrate ~10^6 coupled Newton-type equations looking for **extremely rare events**

RARE EVENT PROBLEMS

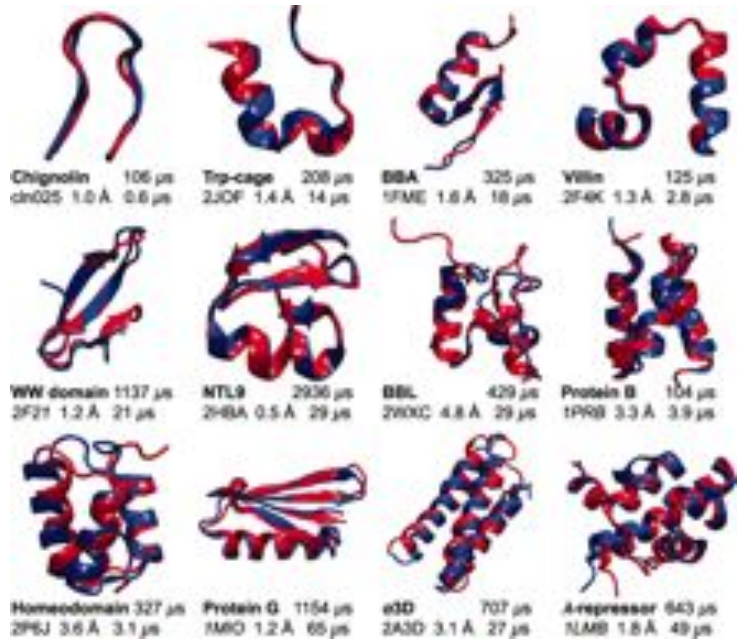




MD YIELDS CORRECT PROTEIN NATIVE STATES

Anton supercomputer
(DES Research)

MD



Science
AAAS

Atomic-Level Characterization of the Structural Dynamics of Proteins
David E. Shaw, *et al.*
Science **330**, 341 (2010);
DOI: 10.1126/science.1187409

How Fast-Folding Proteins Fold

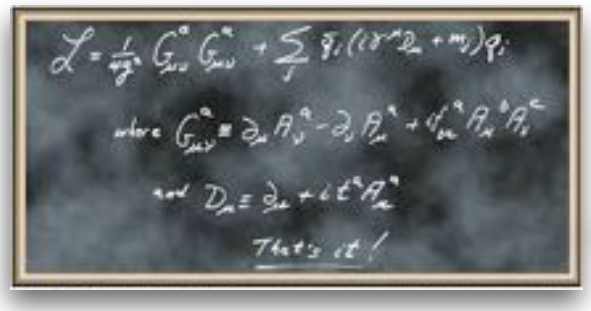
Kresten Lindorff-Larsen,[1*†] Stefano Piana,[1*†] Ron O. Dror,[1] David E. Shaw[1,2†]

ZOOLOGY OF ENHANCED SAMPLING METHODS

Markov State Models, Milestoning, Transition Path Sampling, Transition Interface Sampling, Forward Flux Sampling, Temperature Accelerated Molecular Dynamics, Metadynamics, Umbrella Sampling, Blue Moon Sampling, String Method,Stochastic Difference, … [and counting]

They are **all too computationally demanding** for many biologically relevant problems.

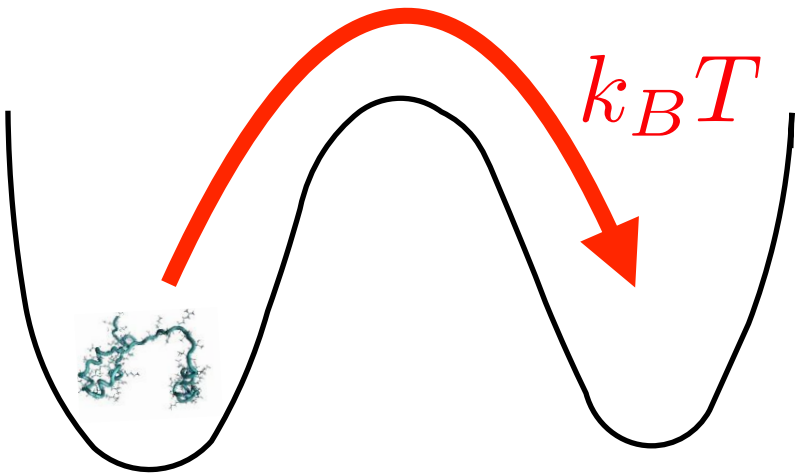
A LONG JOURNEY



A USEFUL ANALOGY

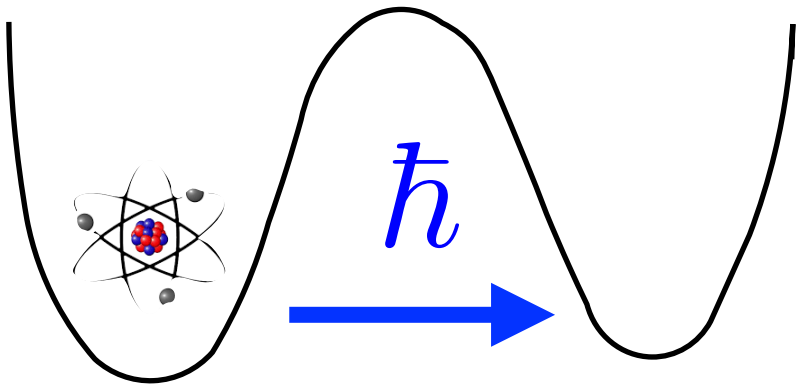
Thermal activation

$(\beta = (K_B T)^{-1})$



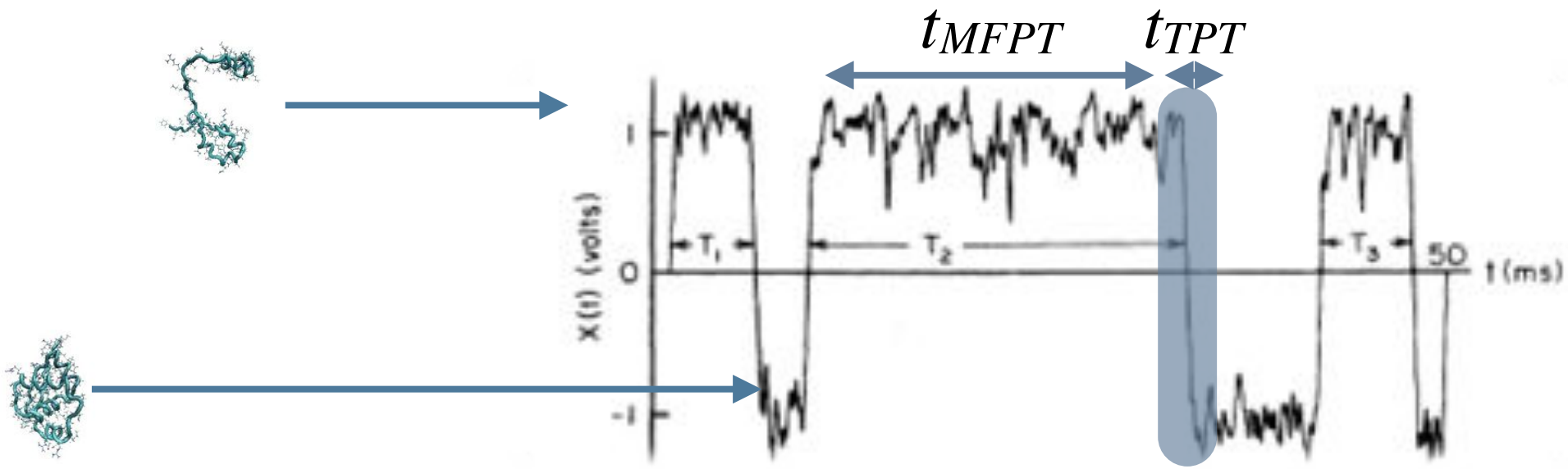
$$P(x_f, t|x_i) = \int_{x_i}^{x_f} \mathcal{D}q \; e^{-\frac{\beta}{4M\gamma} \int_0^t d\tau (M\ddot{q} + M\gamma\dot{q} + \nabla U(q))^2}$$

Quantum tunneling



$$K_E(x_f, t|x_i) = \int_{x_i}^{x_f} \mathcal{D}q \; e^{-\frac{1}{\hbar} \int_0^t d\tau \left(\frac{M}{2}\dot{q}^2 + U(q) \right)}$$

ADVANTAGES



$$t_{TPT} \sim \tau_0 \log\left[\log\left(\frac{t_{MFPT}}{\tau_0}\right)\right]$$

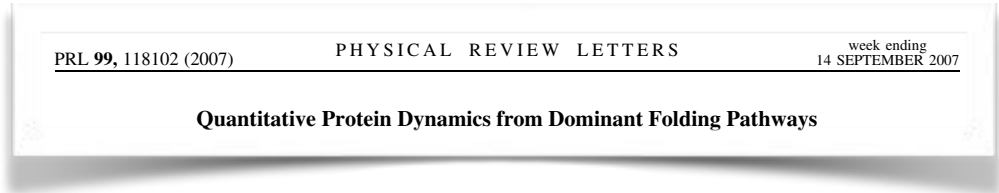
VARIATIONAL APPROACHES TO TRANSITION PATH SAMPLING

Dominant **R**eaction **P**athways


PRL **97,** 108101 (2006) PHYSICAL REVIEW LETTERS week ending 8 SEPTEMBER 2006

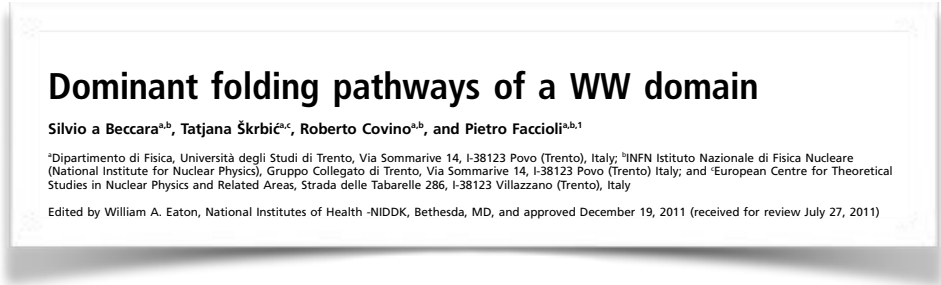
Dominant Pathways in Protein Folding

(2005)


PRL **99,** 118102 (2007) PHYSICAL REVIEW LETTERS week ending 14 SEPTEMBER 2007

Quantitative Protein Dynamics from Dominant Folding Pathways

(2006)


Dominant folding pathways of a WW domain

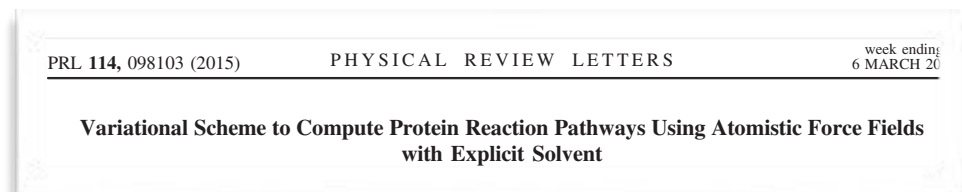
Silvio a Beccara[a,b], Tatjana Škrbić[a,c], Roberto Covino[a,b], and Pietro Faccioli[a,b,1]

[a]Dipartimento di Fisica, Università degli Studi di Trento, Via Sommarive 14, I-38123 Povo (Trento), Italy; [b]INFN Istituto Nazionale di Fisica Nucleare (National Institute for Nuclear Physics), Gruppo Collegato di Trento, Via Sommarive 14, I-38123 Povo (Trento) Italy; and [c]European Centre for Theoretical Studies in Nuclear Physics and Related Areas, Strada delle Tabarelle 286, I-38123 Villazzano (Trento), Italy

Edited by William A. Eaton, National Institutes of Health -NIDDK, Bethesda, MD, and approved December 19, 2011 (received for review July 27, 2011)

(2012)

Bias **F**unctional **A**pproach


PRL **114,** 098103 (2015) PHYSICAL REVIEW LETTERS week ending 6 MARCH 20

Variational Scheme to Compute Protein Reaction Pathways Using Atomistic Force Fields with Explicit Solvent

(2015)

Self **C**onsistent **P**ath **S**ampling

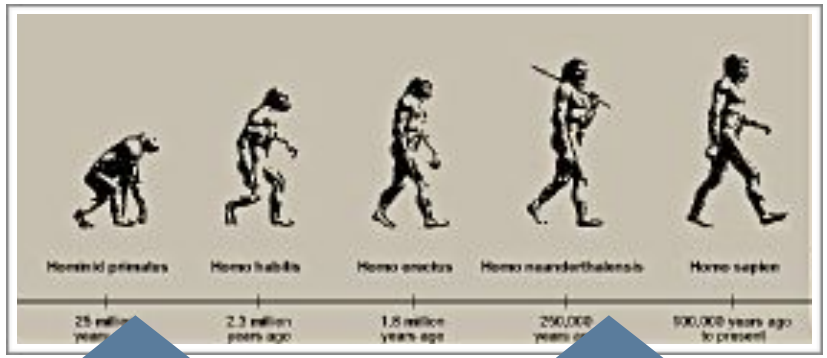

THE JOURNAL OF CHEMICAL PHYSICS **147**, 064108 (2017)

Self-consistent calculation of protein folding pathways

S. Orioli, S. a Beccara, and P. Faccioli[a)]

(2017)

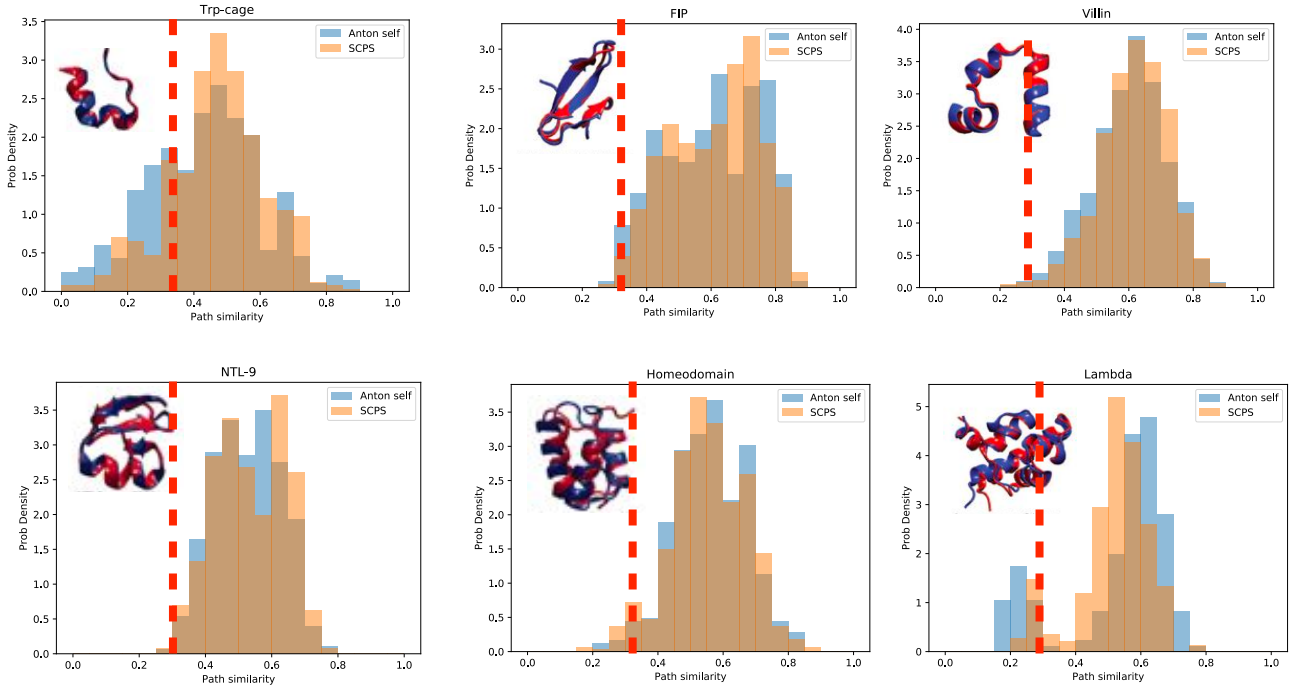
HUGE COMPUTATIONAL GAIN



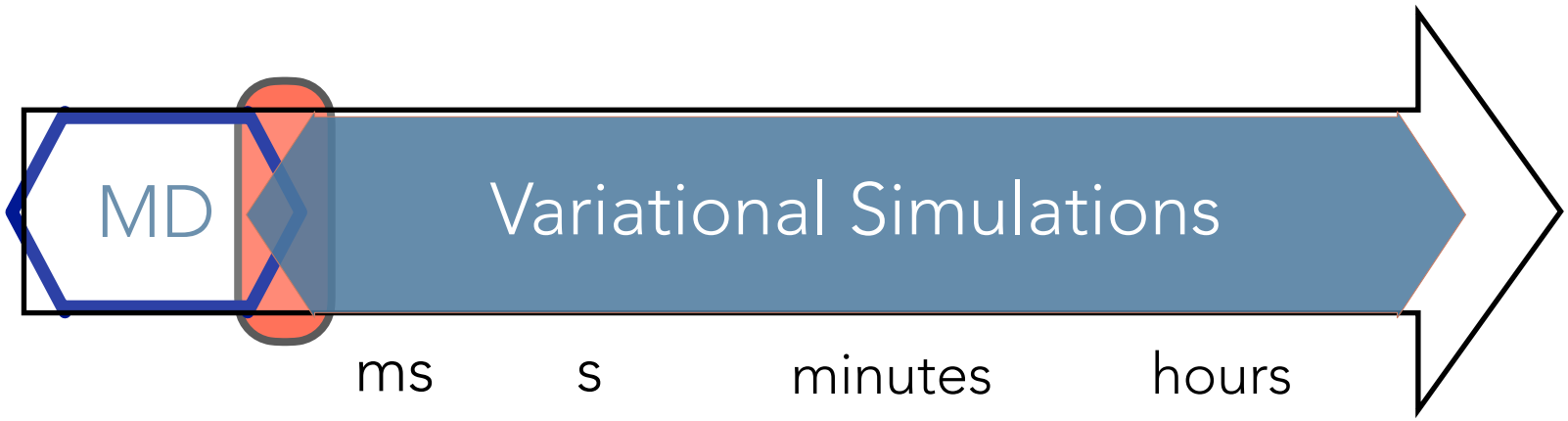
Using top all-purpose supercomputers

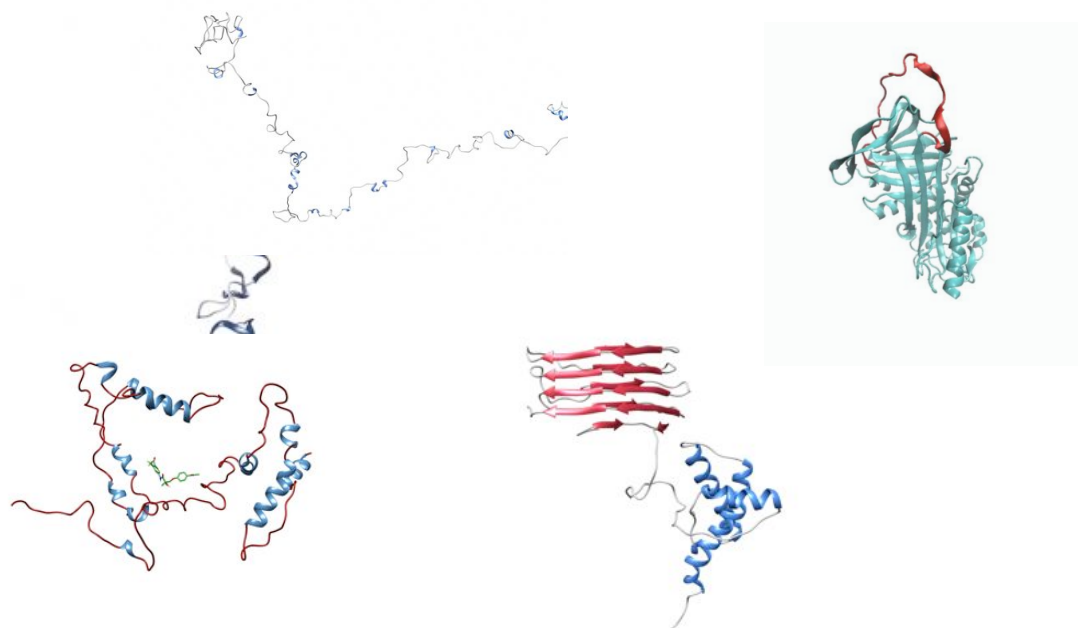
Using top special-purpose supercomputer

VALIDATING SCPS AGAINST MD

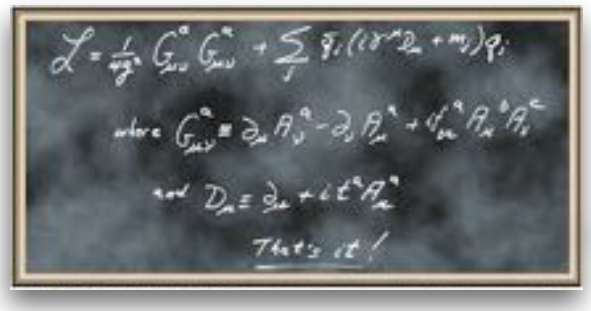


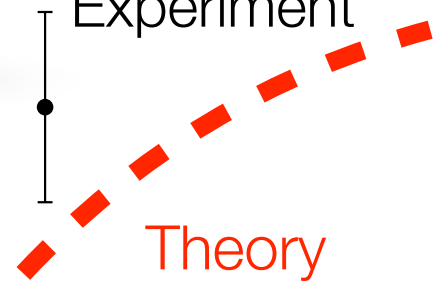
VENTURING INTO THE BIO-ZONE



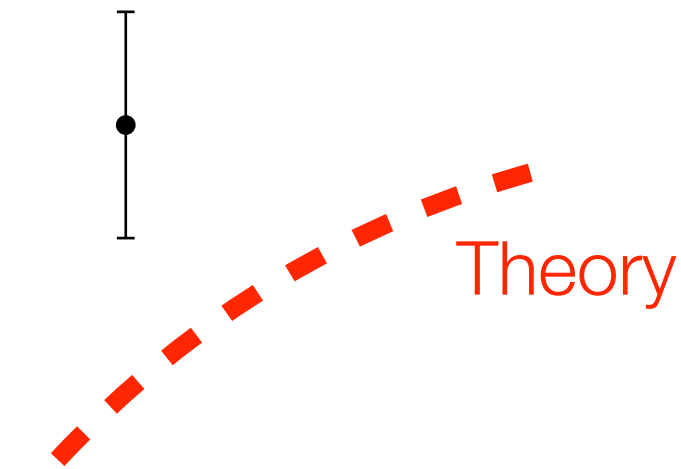


A LONG JOURNEY





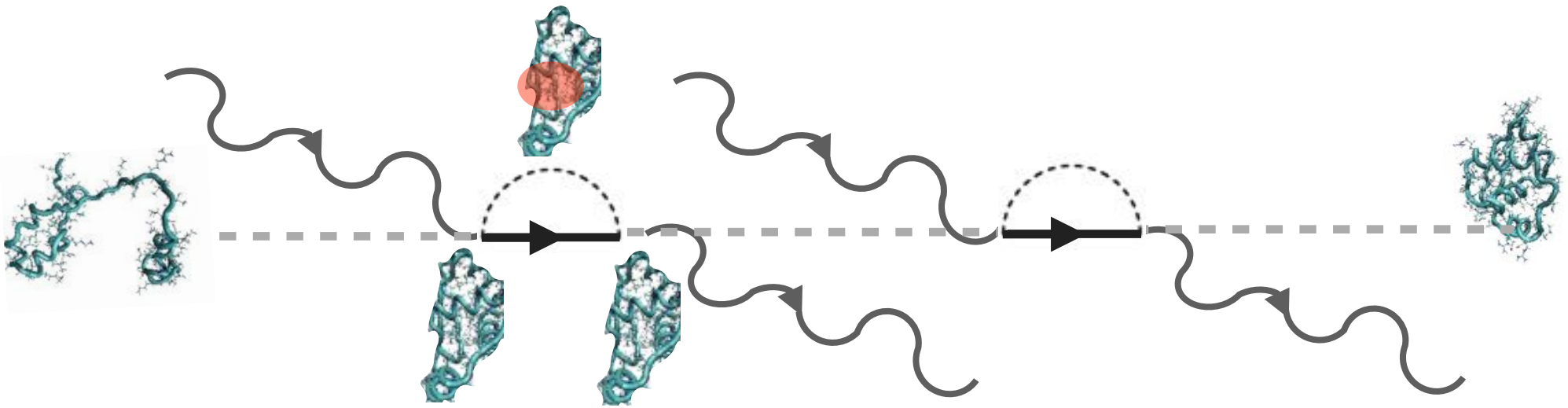
VALIDATION AGAINST EXPERIMENT



Challenge:

Most available techniques provide only indirect probes, we seek for **direct validation**

TIME-DEPENDENT LINEAR SPECTROSCOPY



Ground state

One exciton

Challenge:

Need a theory for **non-equilibrium dynamics** of **quantum** electronic excitations in conformationally evolving proteins

MOLECULAR QUANTUM FIELD THEORY*

$$Z = \int \mathcal{D}\psi\mathcal{D}\bar{\psi} \int \mathcal{D}q \; e^{-S_{MQFT}[\psi,\bar{\psi},q]}$$

$$S_{MQFT}[q,\psi,\bar{\psi}] = S_{OM}[q] + S_S[\psi,\bar{\psi}] + S_{int}[q,\psi,\bar{\psi}]$$

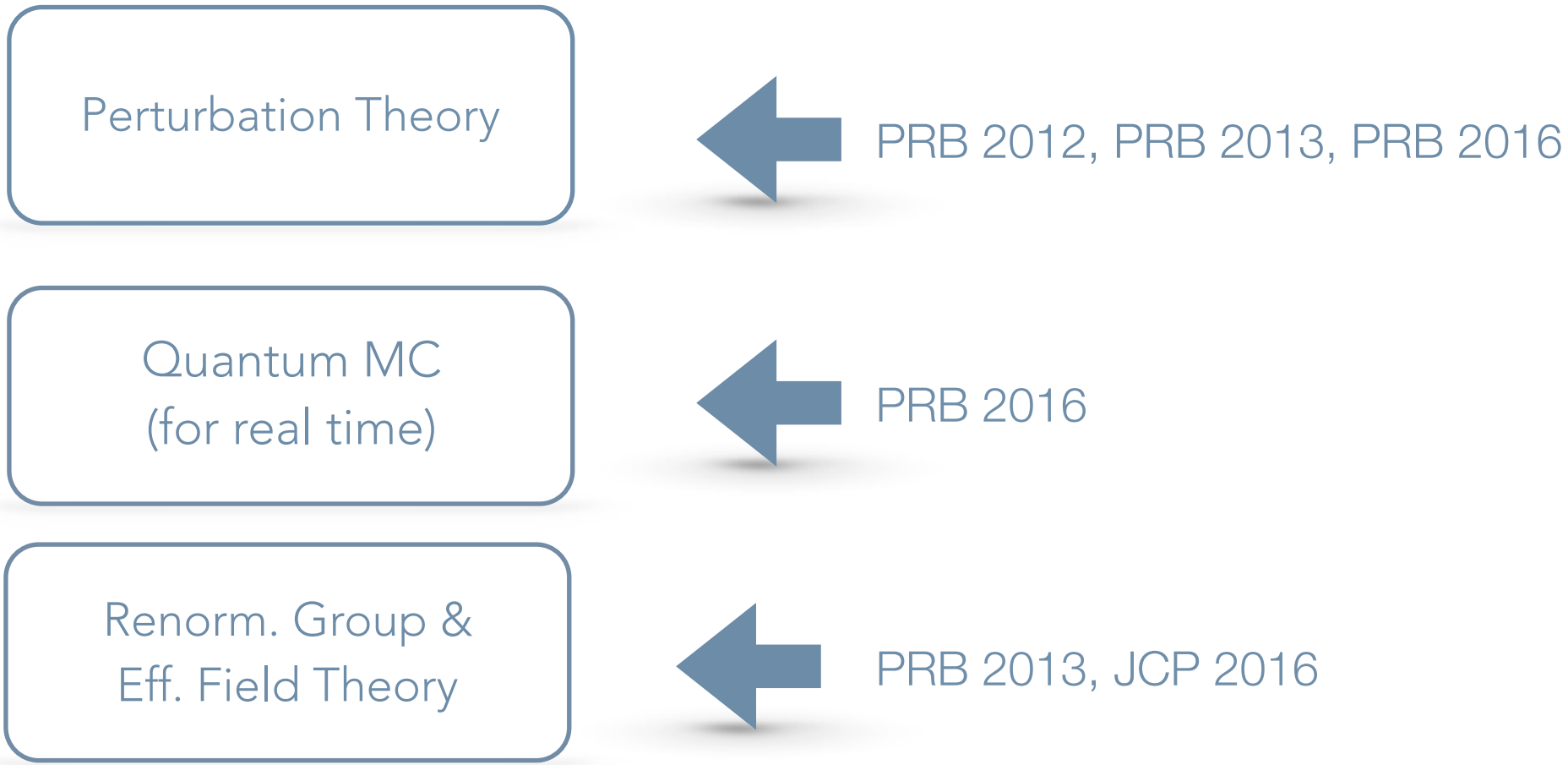
$$S_{OM}[q] = \int_0^t d\tau \frac{\beta}{4M\gamma} \left(M\ddot{q} + M\gamma\dot{q} + \nabla U(q)\right)^2$$

$$S_S[\psi,\bar{\psi}] = \sum_{n,m} \int_0^t d\tau \bar{\psi}_n(\tau) \left(i\hbar\partial_t - h^0_{nm}\right) \psi_m(\tau)$$

$$S_{int}[q,\psi,\bar{\psi}] = \sum_{nm} \sum_i \int_0^t d\tau \; f^i_{nm} \; \bar{\psi}_n \psi_m \, \delta q_i$$

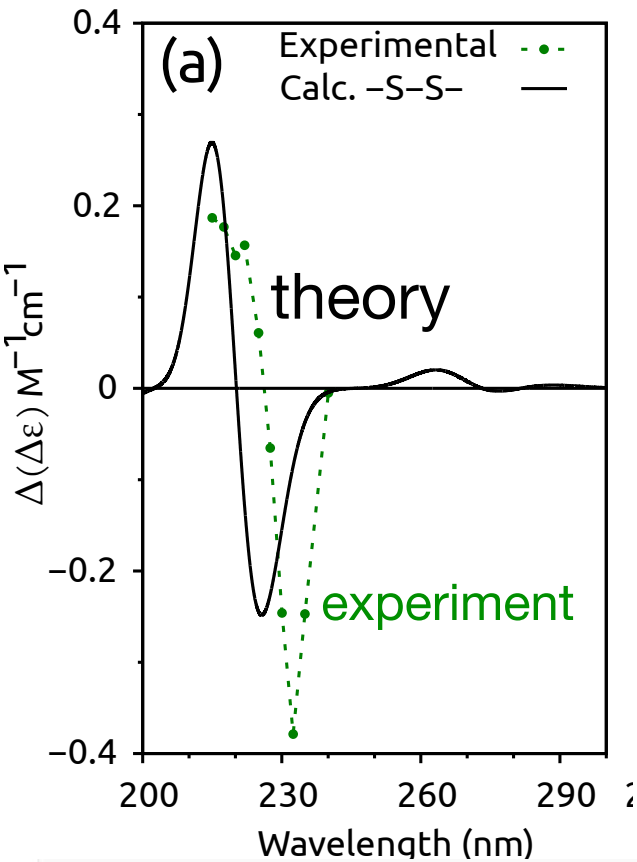
P. Faccioli & E. Schneider (2013-2016)

SOLVING MQFT: AN ARSENAL OF METHODS



EXAMPLES OF DIRECT COMPARISON WITH EXPERIMENTS

Time resolved near UV CD*



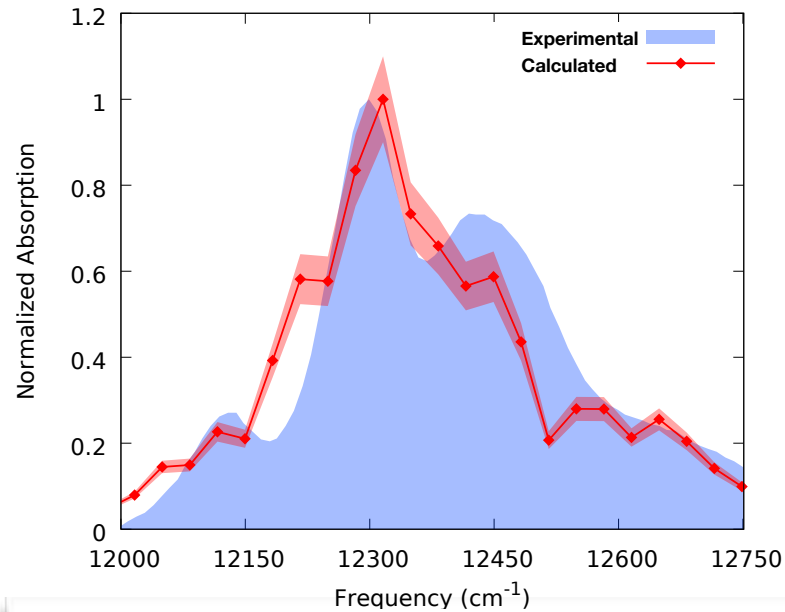
J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

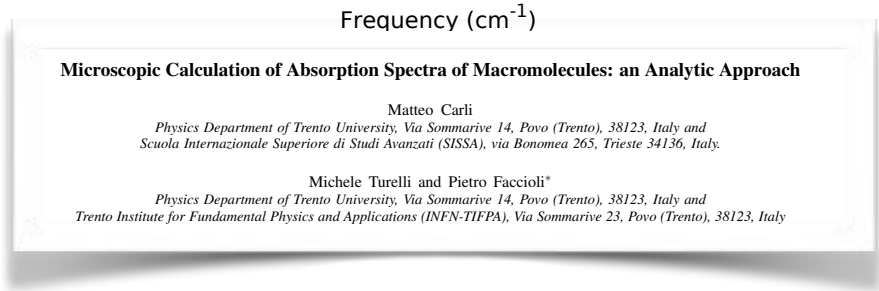
Cite This: J. Am. Chem. Soc. 2018, 140, 3674–3682

Atomic Detail of Protein Folding Revealed by an Ab Initio Reappraisal of Circular Dichroism

Alan Ianeselli,[†] Simone Orioli,[‡,∥] Giovanni Spagnolli,[†] Pietro Faccioli,[*,‡,∥] Lorenzo Cupellini,[§] Sandro Jurinovich,[§] and Benedetta Mennucci[*,§]

Linear absorption spectrum





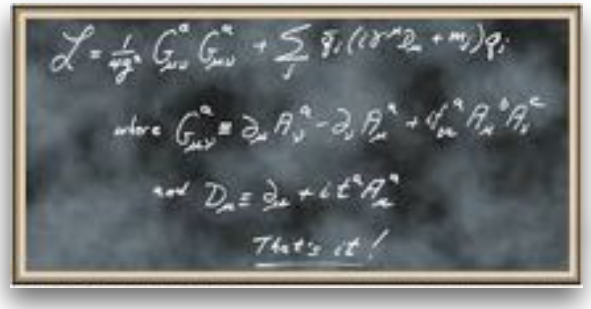
Microscopic Calculation of Absorption Spectra of Macromolecules: an Analytic Approach

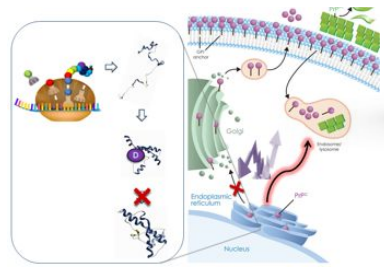
Matteo Carli
Physics Department of Trento University, Via Sommarive 14, Povo (Trento), 38123, Italy and Scuola Internazionale Superiore di Studi Avanzati (SISSA), via Bonomea 265, Trieste 34136, Italy.

Michele Turelli and Pietro Faccioli*
Physics Department of Trento University, Via Sommarive 14, Povo (Trento), 38123, Italy and Trento Institute for Fundamental Physics and Applications (INFN-TIFPA), Via Sommarive 23, Povo (Trento), 38123, Italy

* with B. Mennucci's Lab (U. Pisa)

A LONG JOURNEY

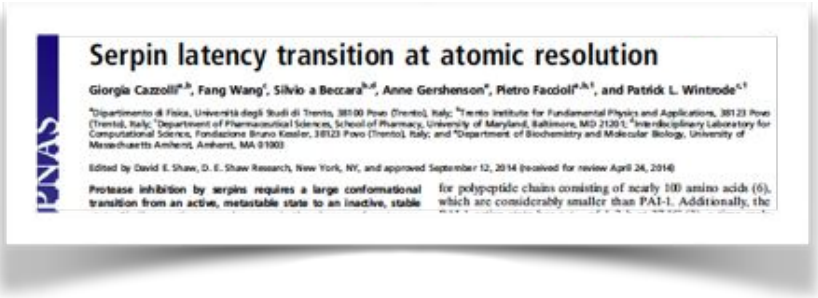




Experiment

Theory

EXPLORING BIOLOGICAL PROCESSES



PNAS

Serpin latency transition at atomic resolution

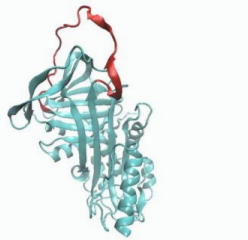
Giorgia Cazzolli[a,b], Fang Wang[c], Silvio a Beccara[b,d], Anne Gershenson[e], Pietro Faccioli[a,b,f], and Patrick L. Wintrode[c,1]

[a]Dipartimento di Fisica, Università degli Studi di Trento, 38100 Povo (Trento), Italy; [b]Trento Institute for Fundamental Physics and Applications, 38123 Povo (Trento), Italy; [c]Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD 21201; [d]Interdisciplinary Laboratory for Computational Science, Fondazione Bruno Kessler, 38123 Povo (Trento), Italy; and [e]Department of Biochemistry and Molecular Biology, University of Massachusetts Amherst, Amherst, MA 01003

Edited by David E. Shaw, D. E. Shaw Research, New York, NY, and approved September 12, 2014 (received for review April 24, 2014)

Protease inhibition by serpins requires a large conformational transition from an active, metastable state to an inactive, stable

for polypeptide chains consisting of nearly 100 amino acids (6), which are considerably smaller than PAI-1. Additionally, the



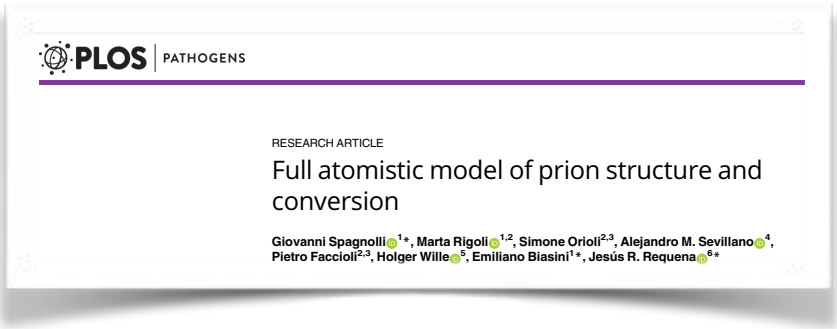
Biophysical Journal

Article

Biophysical Society

All-Atom Simulations Reveal How Single-Point Mutations Promote Serpin Misfolding

Fang Wang,[1] Simone Orioli,[2,3] Alan Ianeselli,[2,3] Giovanni Spagnolli,[2,3] Silvio a Beccara,[2,3] Anne Gershenson,[4,*] Pietro Faccioli,[2,3,*] and Patrick L. Wintrode[1,*]

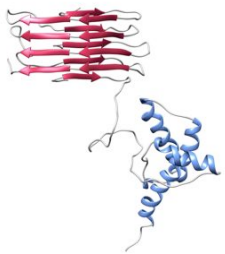


PLOS | PATHOGENS

RESEARCH ARTICLE

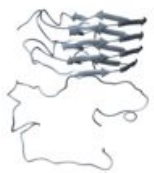
Full atomistic model of prion structure and conversion

Giovanni Spagnolli[1]*, Marta Rigoli[1,2], Simone Orioli[2,3], Alejandro M. Sevillano[4], Pietro Faccioli[2,3], Holger Wille[5], Emiliano Biasini[1]*, Jesús R. Requena[6]*



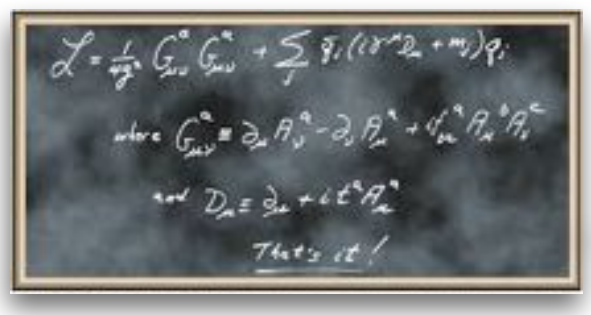
All-Atom Simulation of the HET-s Prion Replication

Luca Terruzzi[1,2]*, Giovanni Spagnolli[2,3]*#, Alberto Boldrini[1,2], Jesús R. Requena[4], Emiliano Biasini[2,3]# and Pietro Faccioli[5,6]#



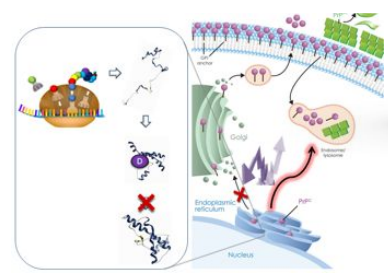
Teaming up with
E. Biasini's lab (DICIBIO)

A LONG JOURNEY



Experiment

Theory



ROLE OF PROTEIN INACTIVATION

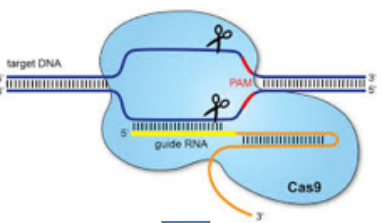
MOST OF BIOLOGICAL FUNCTIONS IN CELLS ARE CARRIED OUT BY **PROTEINS**

MOST OF MEDICINAL CHEMISTRY IS BASED ON
INHIBITING BIOLOGICAL FUNCTIONS OF PROTEINS

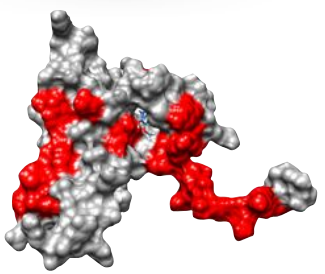
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING

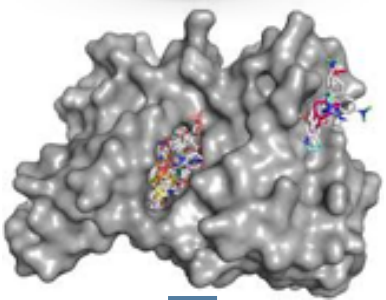
patent file # 102018000007535 (with E. Biasini)

DNA → mRNA → Ribosome → Protein folding → Protein function



RNA silencing





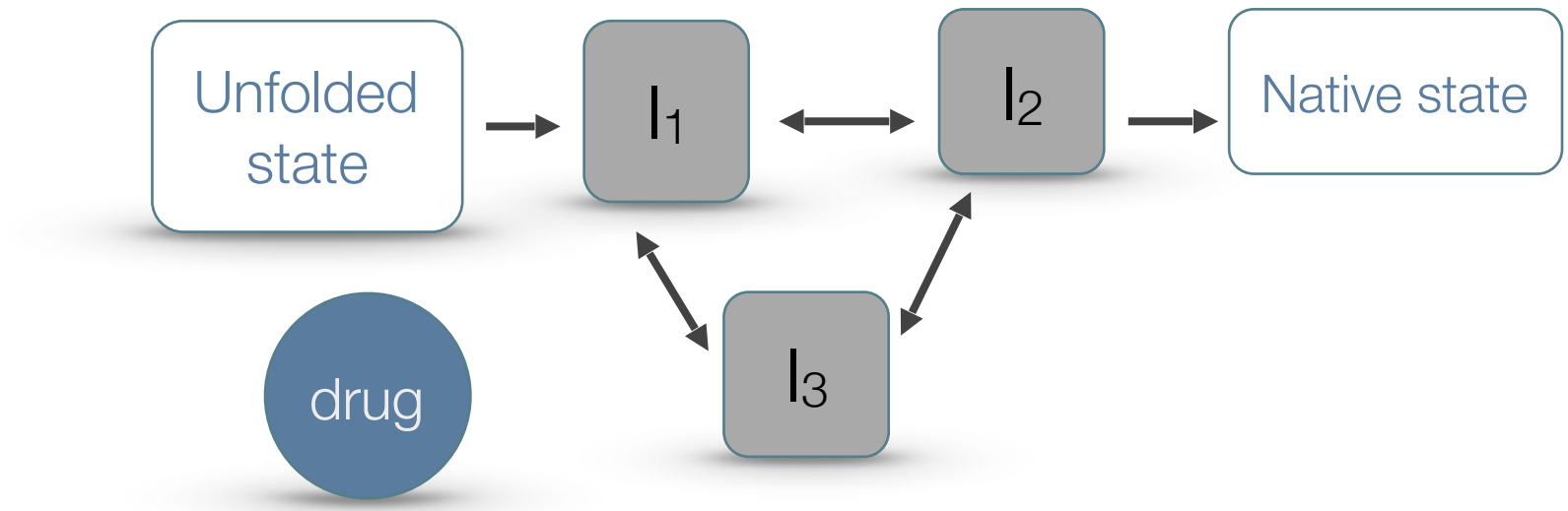
Eliminating protein from genome

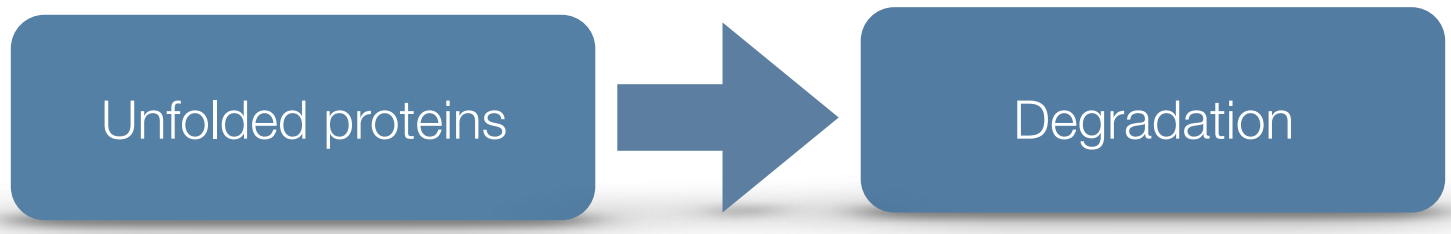
Suppressing transcription

Suppressing folding

Imparing function

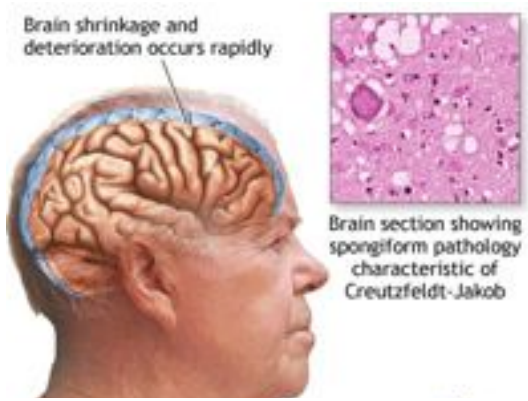
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING





A FIRST VALIDATION

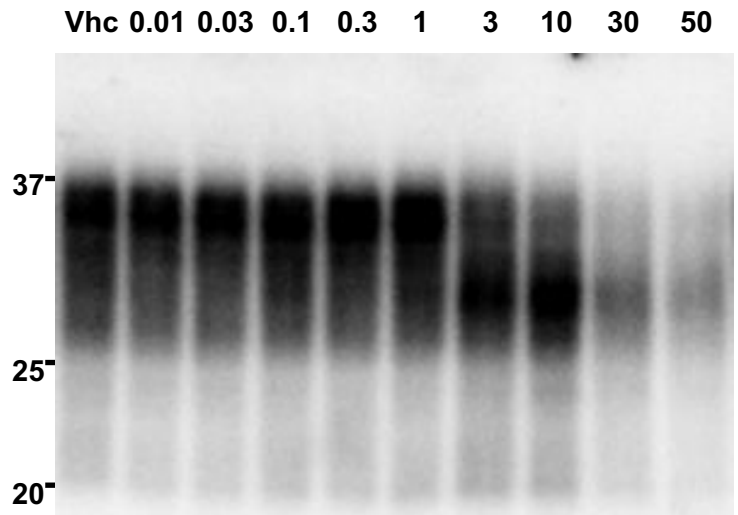
Inactivation of Cellular Prion protein

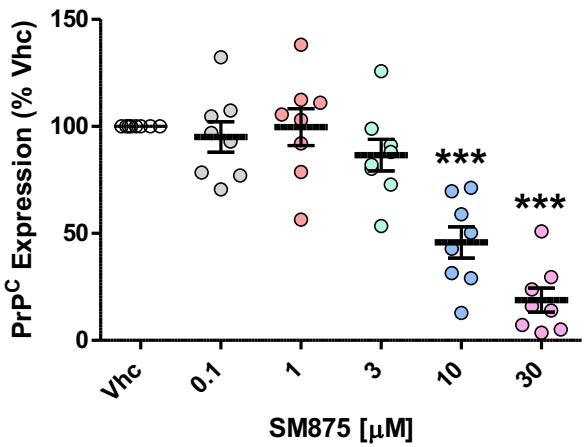


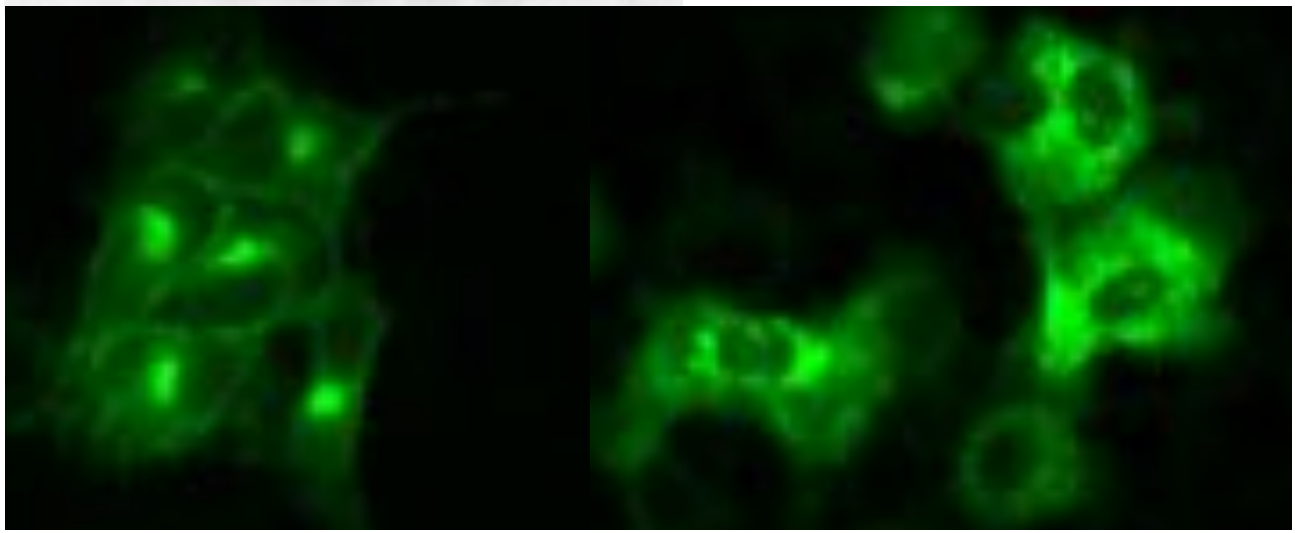
PHARMACOLOGICAL PROTEIN INACTIVATION BY TARGETING FOLDING INTERMEDIATES

Giovanni Spagnolli, Tania Massignan, Andrea Astolfi, Silvia Biggi, Paolo Brunelli, Michela Libergoli, Alan Ianeselli, Simone Orioli, Alberto Boldrini, Luca Terruzzi, Giulia Maietta, Marta Rigoli, Nuria Lopez Lorenzo, Leticia C. Fernandez, Laura Tosatto, Luise Linsenmeier, Beatrice Vignoli, Gianluca Petris, Dino Gasparotto, Maria Pennuto, Graziano Guella, Marco Canossa, Hermann Clemens Altmeppen, Graziano Lolli, Stefano Biressi, Manuel Martin Pastor, Jesús R. Requena, Ines Mancini, Maria Letizia Barreca, Pietro Faccioli, Emiliano Biasini

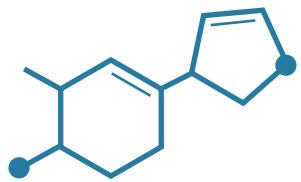
doi: https://doi.org/10.1101/2020.03.31.018069

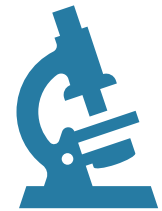


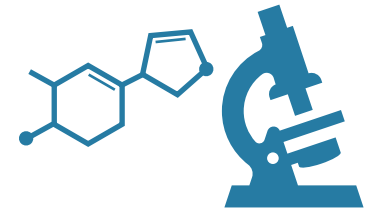




PPI-FIT PIPELINE







Computing the folding pathways characterizing intermediate states

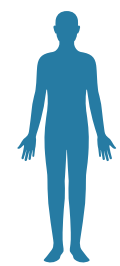
In-silico virtual screening on folding intermediate targets

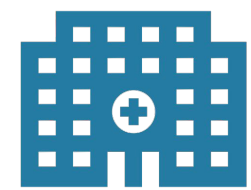
in-vitro evaluation of the effect of the selected compounds on protein expression

Refinement SAR, pharmaco-kinetics, ...

FINAL GOAL

Preclinical and clinical trials





Slide courtesy of Sibylla Biotech SRL

Joining Forces against **COVID-19**

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FONDAZIONE Telethon

Pietro Faccioli

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UNIVERSITÀ DI TRENTO

INFN

Istituto Nazionale di Fisica Nucleare

30.000 cores in 8 data centers

Lidia Pieri

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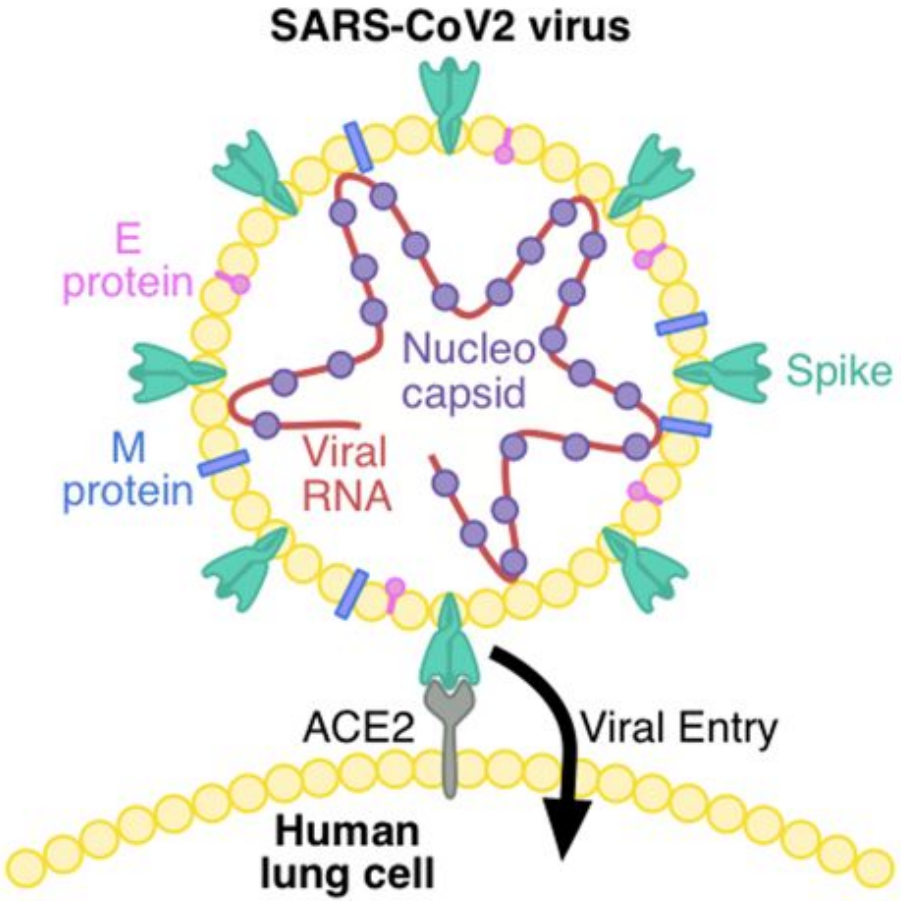
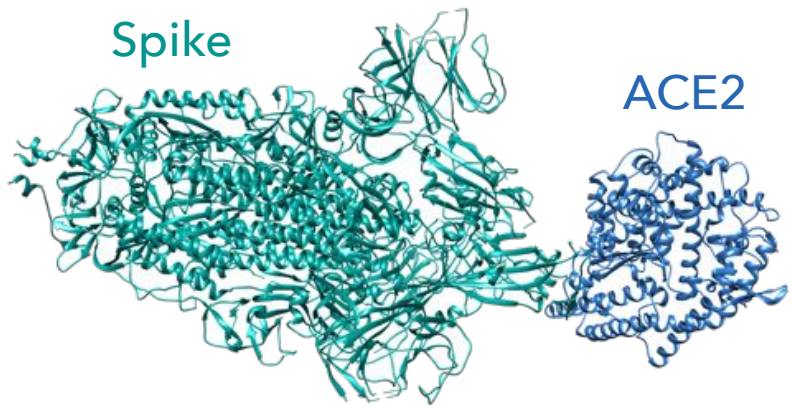
Tania Massignan

Luca Terruzzi

Andrea Astolfi

SARS-CoV-2 Replication





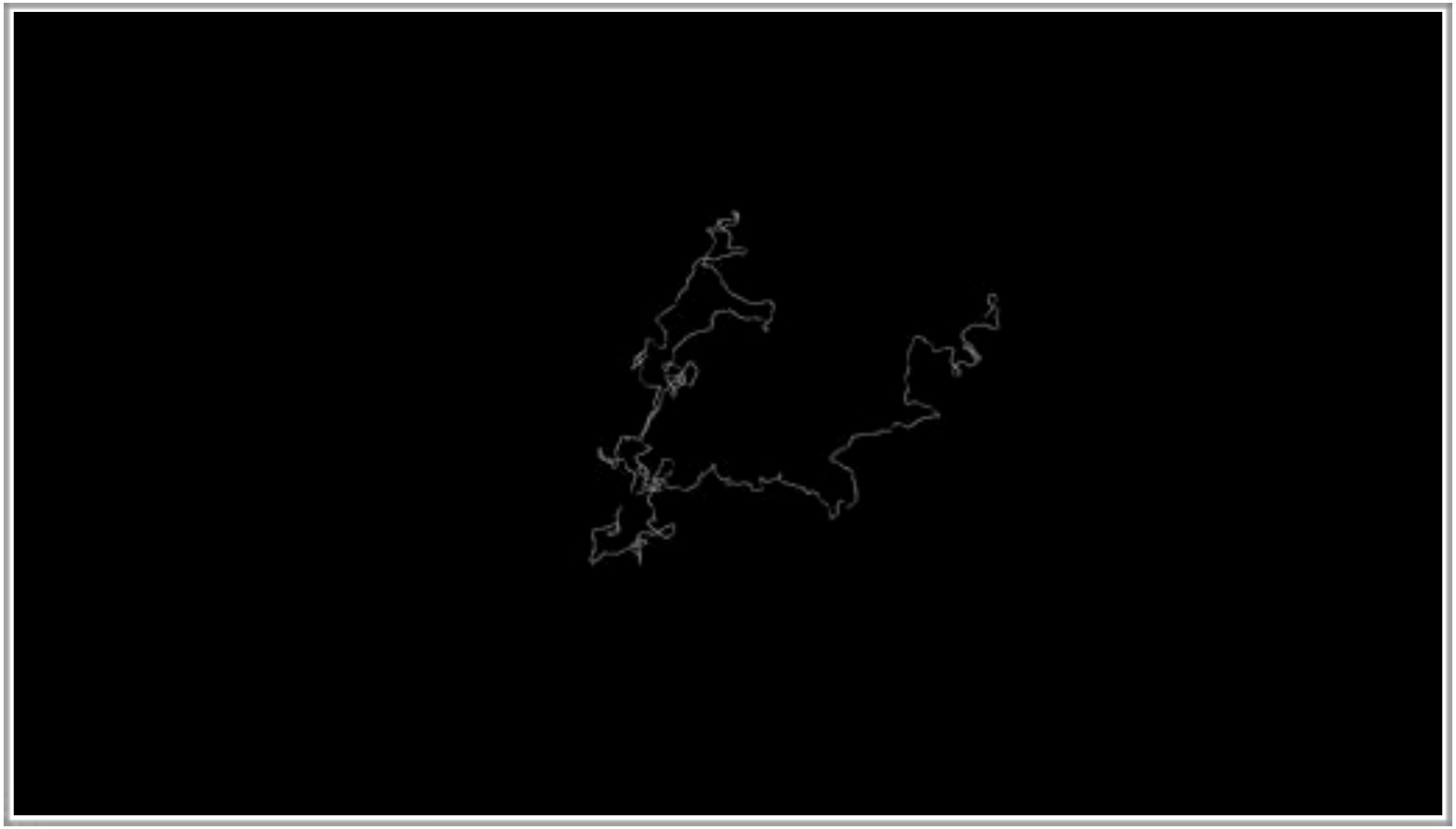
Goals:

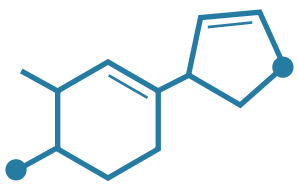
Repurposing of approved drugs!

Looking for suppressors of ACE2 expression levels

Figure taken from:
https://theconversation.com/where-are-we-at-with-developing-a-vaccine-for-coronavirus-134784

PPI-FIT ON ACE2



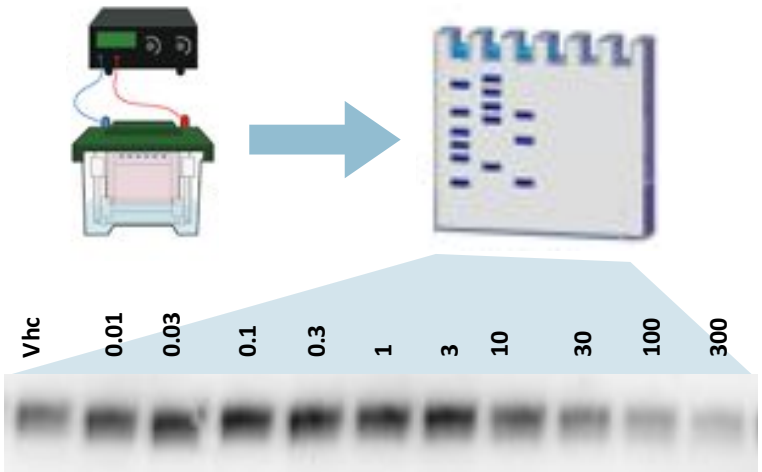


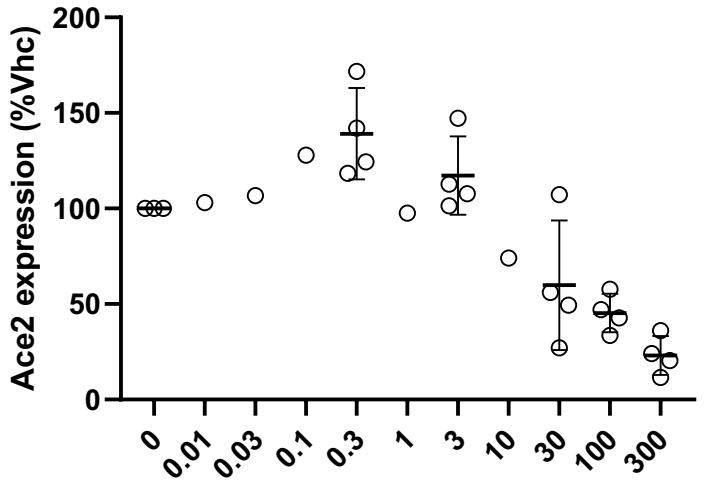
Out of 9000 candidates, we found 35 molecules binding in-silico the intermediate. Validation experiments on cellular bio-assays are ongoing.

BREAKING NEWS!! (17/05/2020)

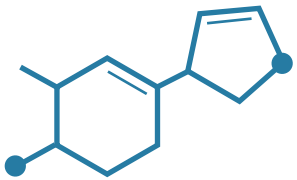
So far, Sibylla Biotech has tested 14 virtual hits

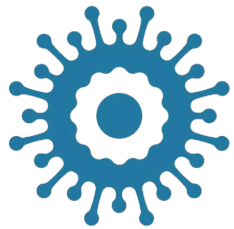
ONE DISPLAYS A **PROMINENT EFFECT** WITH CLEAR **DOSE-RESPONSE** RELATIONSHIP AND VERY **LOW TOXICITY**





PPI-FIT Pipeline





ACE-2 folding pathway reconstruction and intermediate state characterization

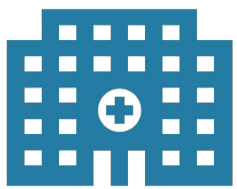
in-silico hit comp ds identification. Virtual screening on FDA approved or investigational drugs

in-vitro evaluat of the effect of the selected compounds on ACE2 expression (degradation wanted)

in-vitro evaluation of the effect of compounds lowering the expression of ACE2 on SARS-COV-2 virus replication

FINAL GOAL

Preclinical and clinical trials



MAIN TAKE-HOME MESSAGES

Fundamental research matters!

The usefulness of **theoretical physics** extends beyond its natural cultural perimeter

Major research infrastructures for fundamental research can be **re-purposed**

Technological transfer can boost research and help advance Science

People

Maria Letizia Barreca PhD

Emiliano Biasini PhD

Pietro Faccioli PhD

Graziano Lolli PhD

Lidia Pieri PhD

Founder - CEO

Giovanni Spagnolli

Founder
Chief Scientist

Alberto Boldrini

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(Computational)

Tania Massignan PhD

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Andrea Astolfi PhD

Consultant
Medicinal Chemist

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TIFPA Trento Institute for Fundamental Physics and Applications

FONDAZIONE Telethon

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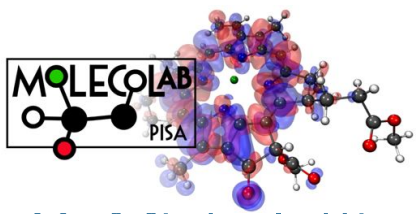

Perugia: L. Barreca

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U. Compostela: J. Raquena

CEA-Saclay: H. Orland

USA:

U. Maryland: P. Wintrode

U. Mass.: A. Gershenson