From Quarks to Drugs

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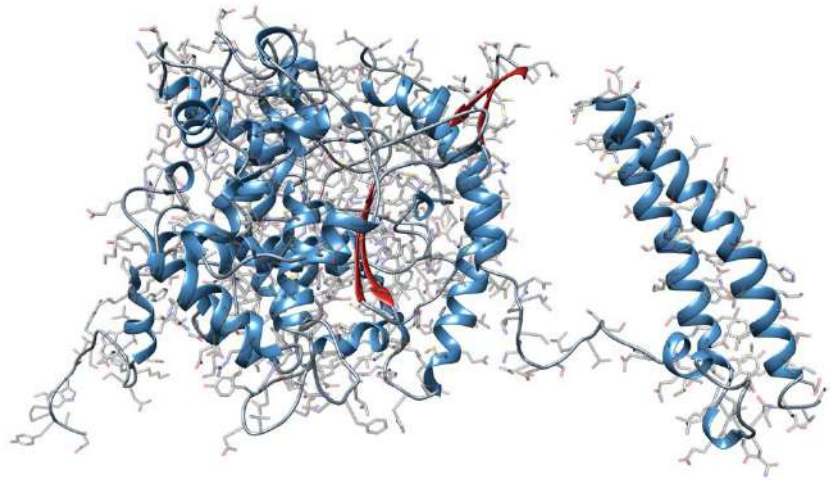
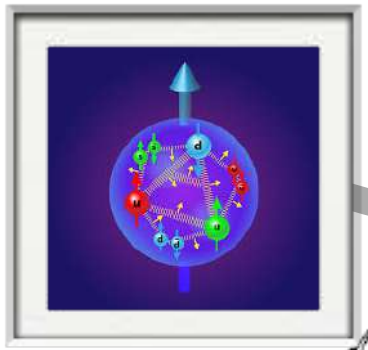
Fundamental Physics
and Applications



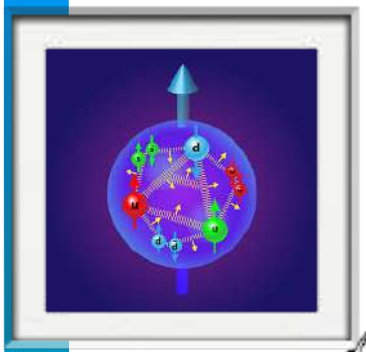
A SCIENTIFIC JOURNEY



Fundamental

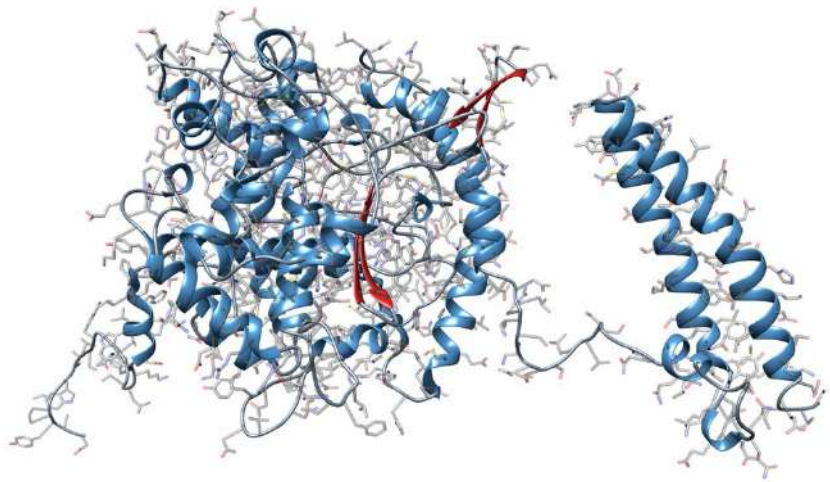
Applied

Physics

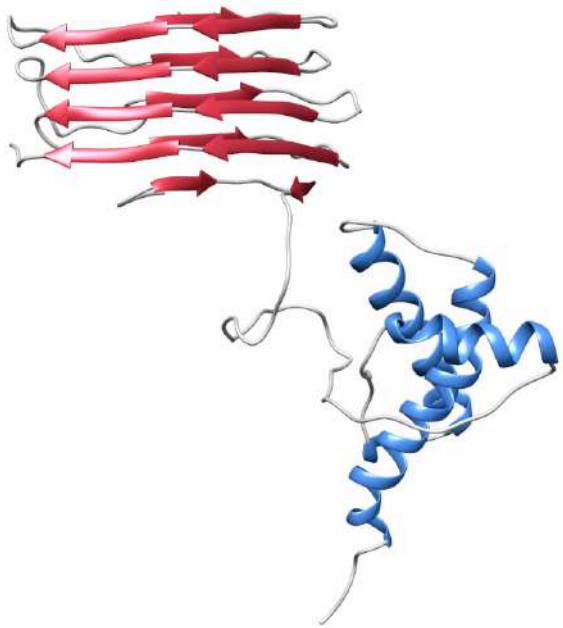


Biology

Prologue: proteins are complex many-body systems.



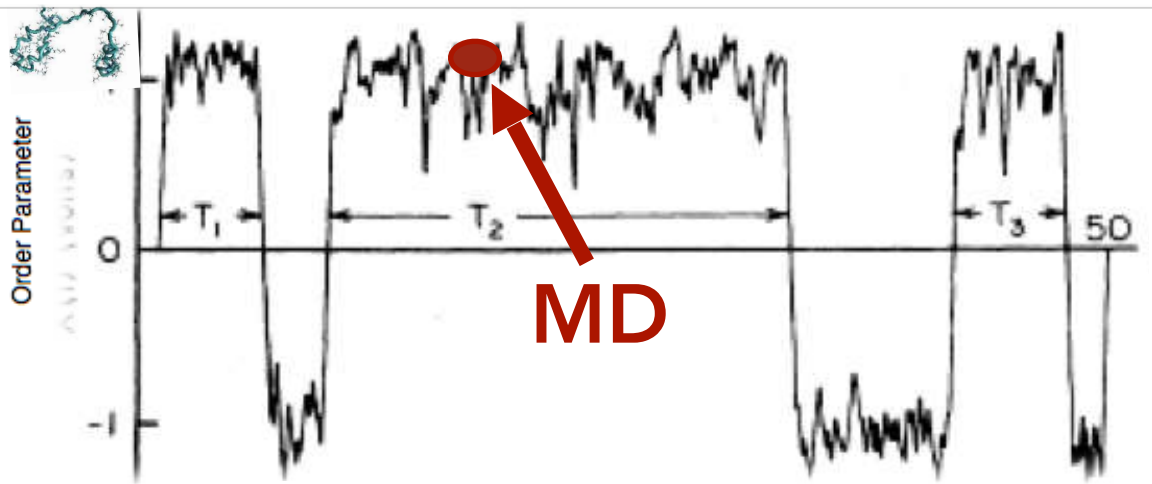
REDUCTIONIST'S APPROACH TO MOLECULAR BIOLOGY

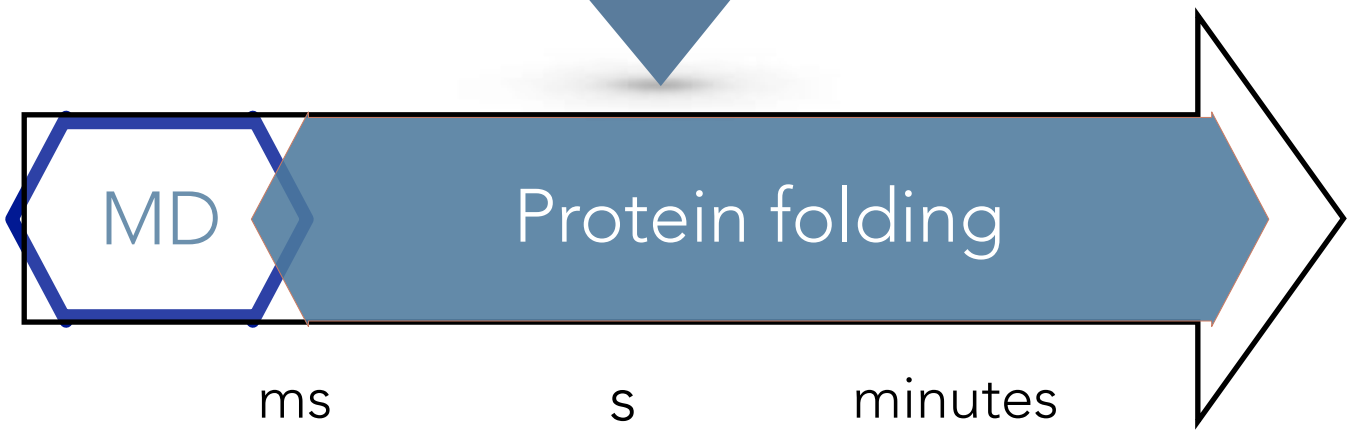


Challenge:

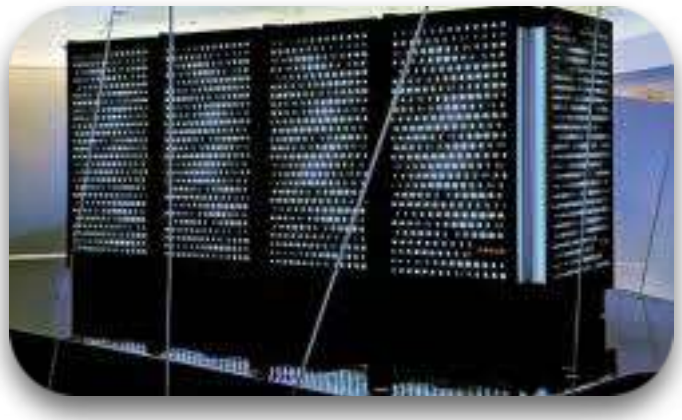
Integrate ~10^6 coupled Newton-type equations looking for **extremely rare events**

RARE EVENT PROBLEMS



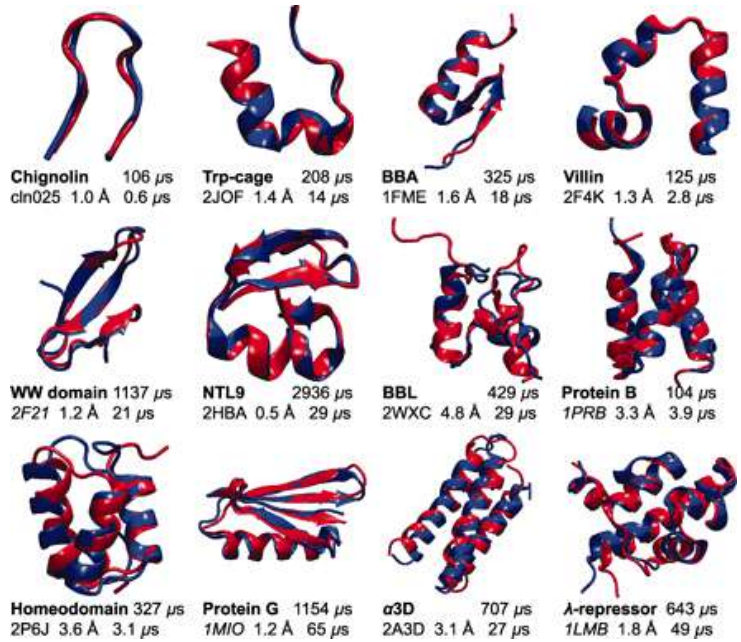


MD YIELDS CORRECT PROTEIN NATIVE STATES



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

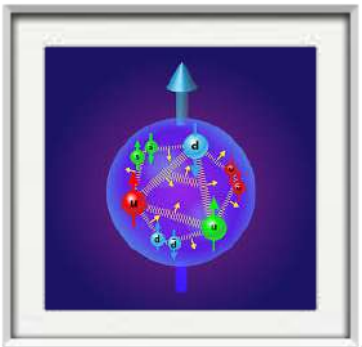
How Fast-Folding Proteins Fold

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

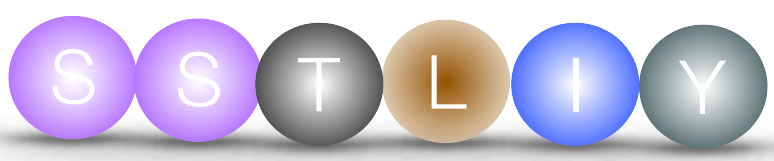
ZOOLOGY OF ENHANCED SAMPLING METHODS

Markov State Models (Folding@Home), 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]

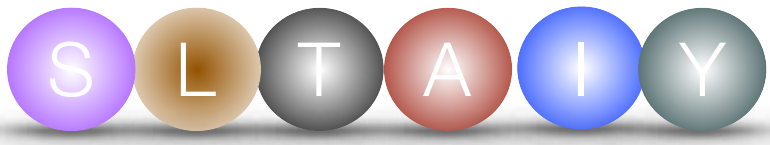
They are **all too computationally demanding** for many biologically relevant problems.



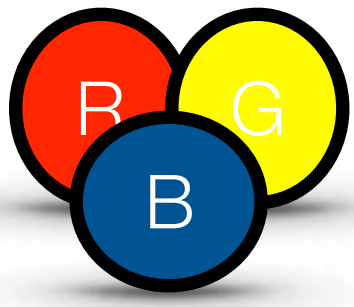
PROTEINS AND HADRONS ARE VERY SPECIAL



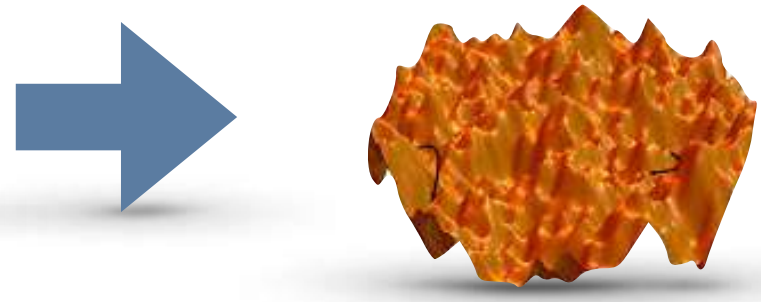
Random polypeptide

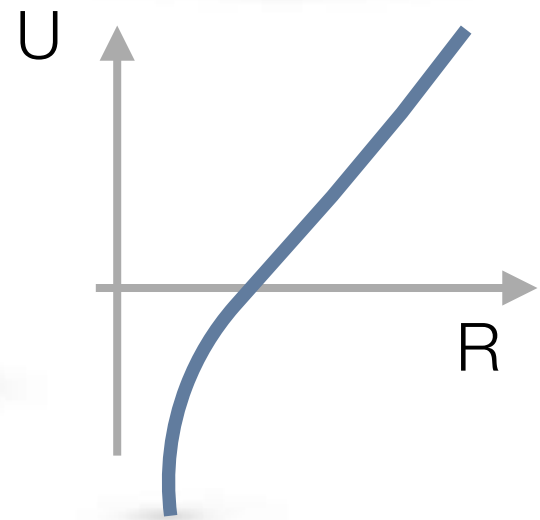


Protein

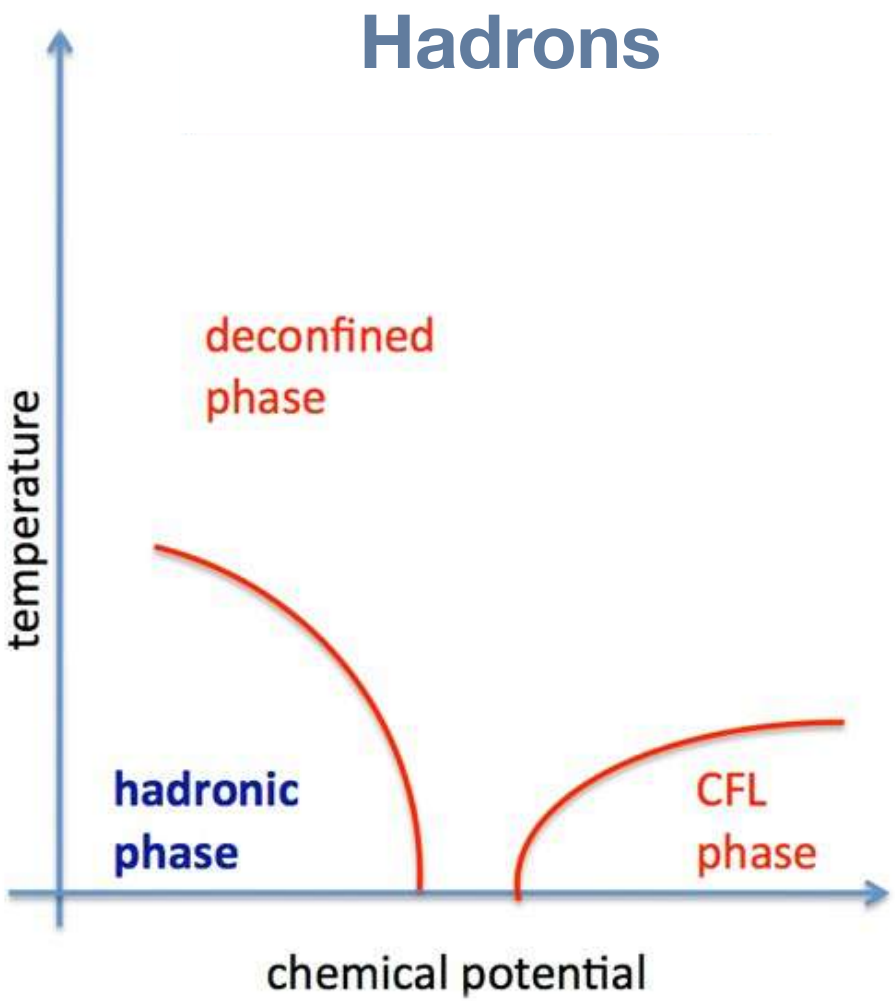


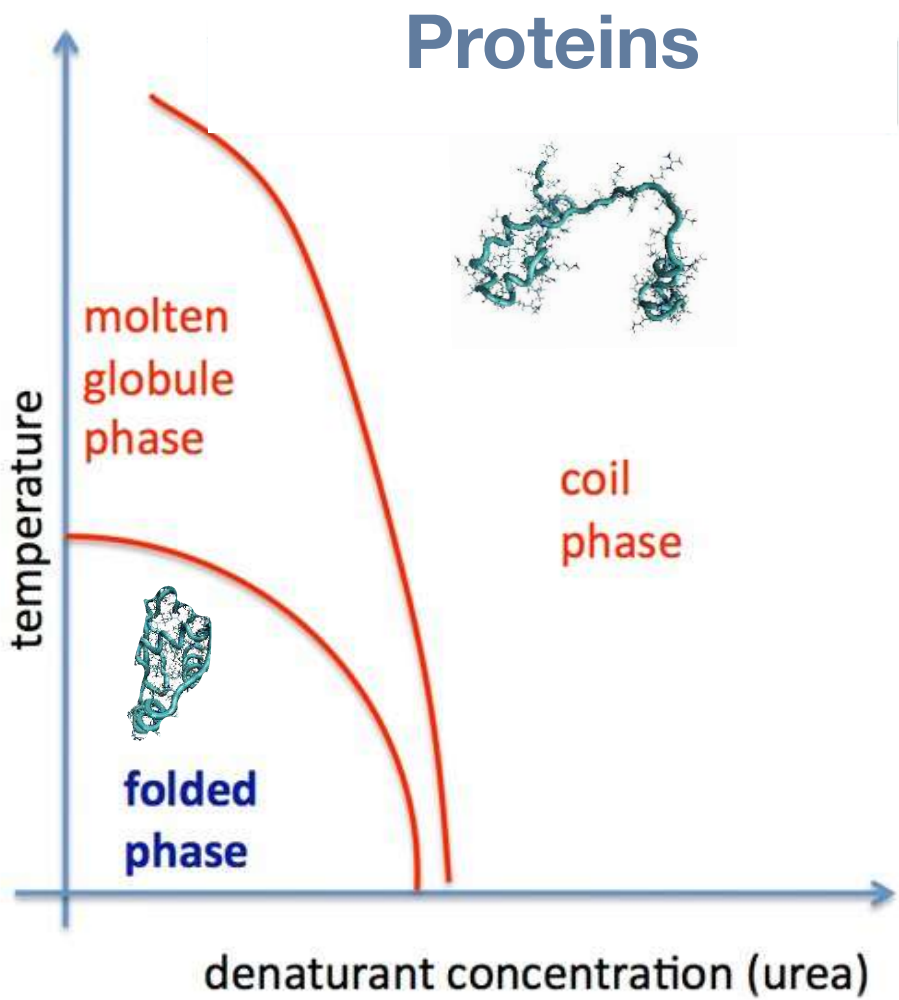
Baryon



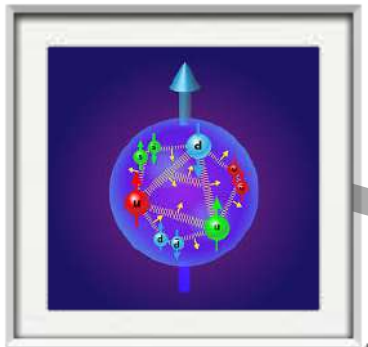


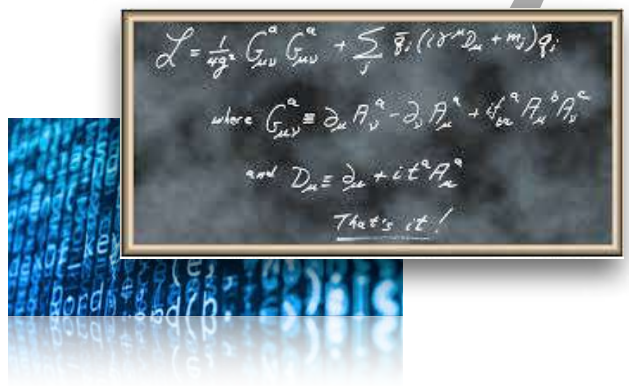
PHASE DIAGRAM





PHASE 1: MATHEMATICAL FORMALISM & HIGH PERFORMANCE COMPUTING





PATH INTEGRAL REPRESENTATION

Hamilton's equations

Langevin equations

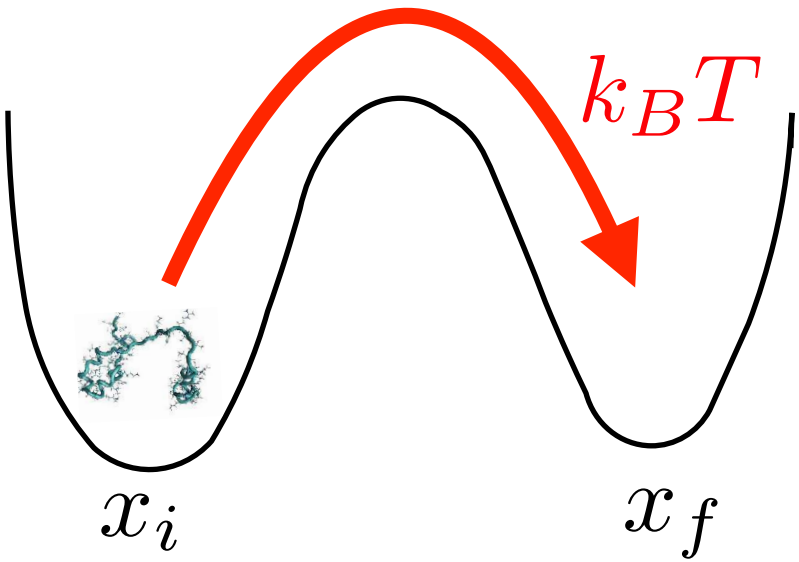
$$M\ddot{\mathbf{r}}_i = -\nabla_i U(\mathbf{R}) - \gamma_i \dot{\mathbf{r}}_i + \eta_i(t)$$

$$P(R_f, t|R_i, 0) = \int_{R_i}^{R_f} \mathcal{D}R \; e^{-\frac{\beta}{4m\gamma}\int_0^t d\tau (m\ddot{R}+m\gamma\dot{R}+\nabla U)^2}$$

A USEFUL ANALOGY

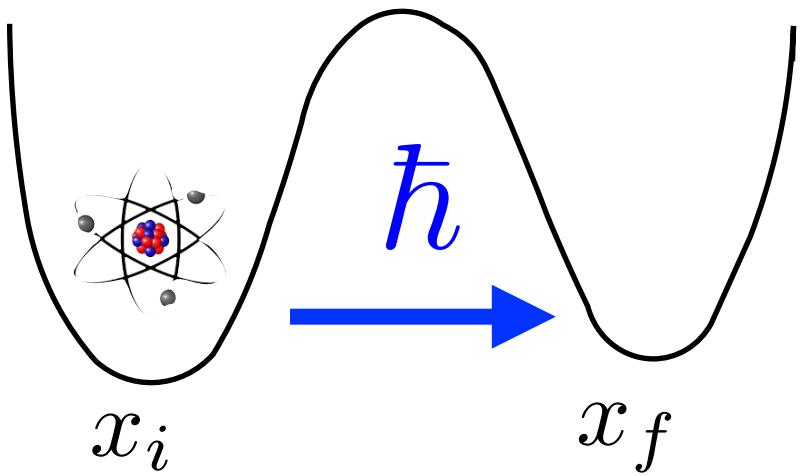
Thermal activation

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



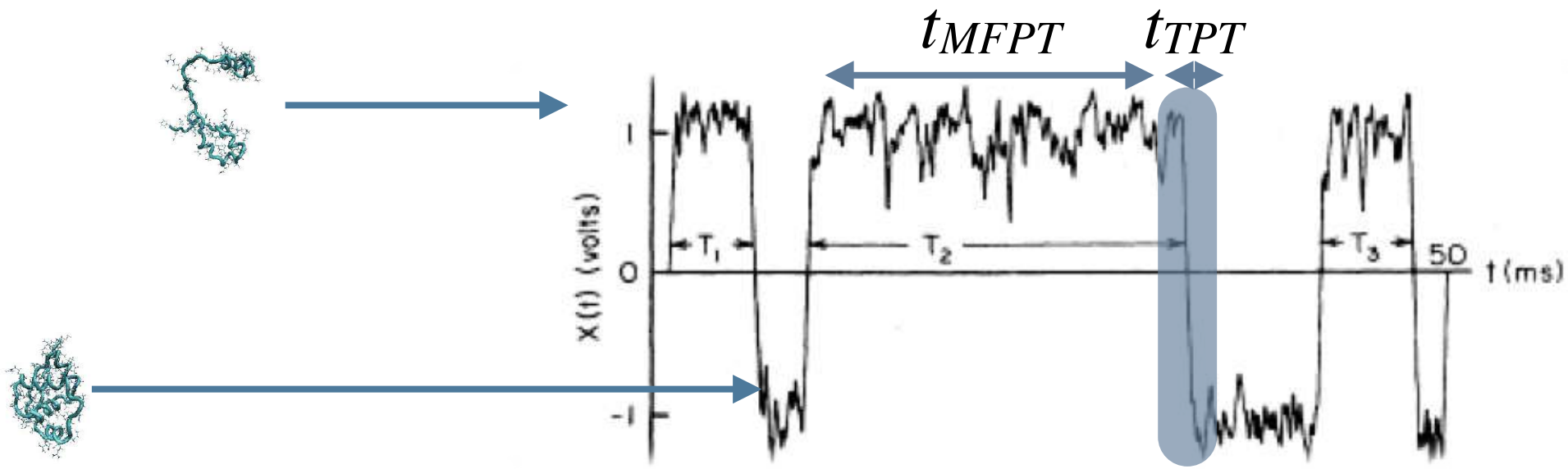
$$P(x_f, t|x_i) = \int_{x_i}^{x_f} \mathcal{D}q \; e^{-\frac{\beta}{4M\gamma} \int_0^t d\tau (M\ddot{q} + M\gamma\dot{q} + \nabla U(q))^2}$$

Quantum tunneling



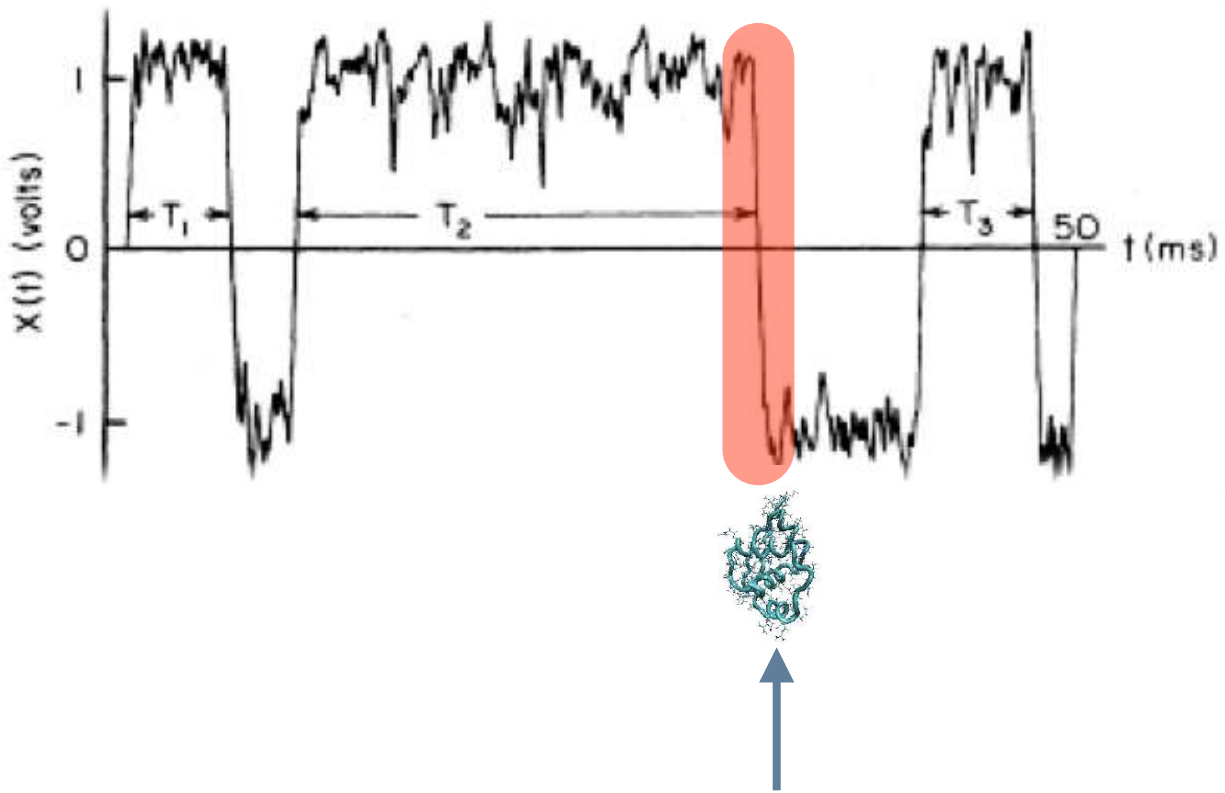
$$K_E(x_f, t|x_i) = \int_{x_i}^{x_f} \mathcal{D}q \; e^{-\frac{1}{\hbar} \int_0^t d\tau \left(\frac{M}{2}\dot{q}^2 + U(q) \right)}$$

ADVANTAGES



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

IS THIS A "FREE LUNCH"?



All atom 3D structure of the native state **are given in input,** not predicted

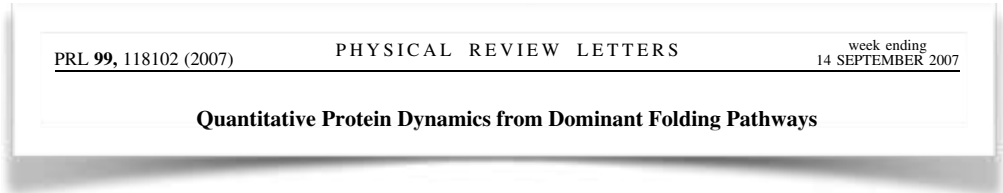
VARIATIONAL APPROACHES TO TRANSITION PATH SAMPLING

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


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

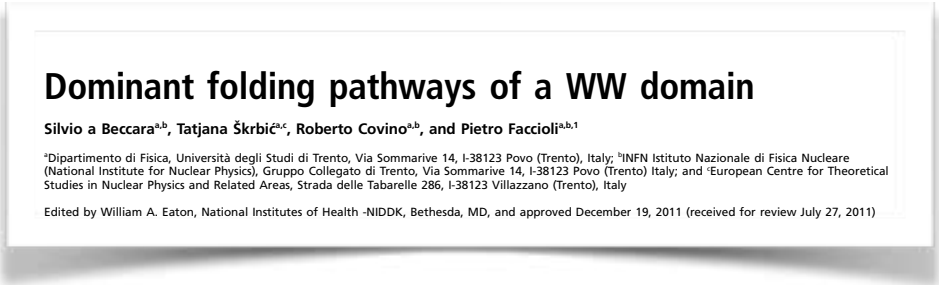
Dominant Pathways in Protein Folding

(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

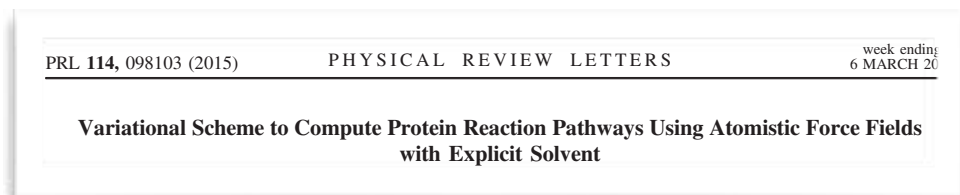
Silvio a Beccara[a,b], Tatjana Škrbić[a,c], Roberto Covino[a,b], and Pietro Faccioli[a,b,1]

[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)

FULLY EXPLOITING THEORETICAL PHYSICS TOOLS

between the Gibbs distribution and the SCR estimate forward- and backward-committors, as in Eq. (A3). Introducing the distribution

$$P^{(P)}(x,t) \equiv \int dx_i\, P^{(P)}(x,t|x_i,0)\, \rho_0(x_i),$$

the density in Eq. (22) reads

$$m_{SCR}(x) = \frac{1}{t_f - \tau_0} \int_{\tau_0}^{t_f} dt\; Q^{(R)}(x, t_f - t) P^{(P)}(x,t).$$

Using the detailed balance condition, we find $P^{(P)} = e^{-\beta U(x)} \frac{1}{Z_R} Q^{(P)}(x,t)$. Then, inserting this result into Eq. we find

$$m_{SCR}(x) = \frac{e^{-\beta U(x)}}{Z_R\,(t_f - \tau_0)} \int_{\tau_0}^{t_f} dt Q^{(R)}(x, t_f - t) Q^{(P)}(x,t).$$

Finally, recalling that $Q^{(R)}(x,t)$ and $Q^{(P)}(x,t)$ are n time-independent in the SCR and using Eqs. (17) and we recover a fundamental result of TPT [cf. Eq. (A Appendix A],

$$m_{SCR}(x) \propto e^{-\beta U(x)}\, q^+_{SCR}(x)\,(1 - q^+_{SCR}(x)\,).$$

Within the same framework, it is possible to d the reactive current in the SCR in complete analogy Eq. (22),

$$J^i_{SCR}(x) = \frac{-D}{t_f - \tau_0} \int_{\tau_0}^{t_f} dt Q^{(R)}(x, t_f - t) \times (\overrightarrow{\nabla} - \overleftarrow{\nabla} + \beta \nabla U(x))\, P^{(P)}(x,t).$$

$$\mathcal{P}_{\rm bias}[X] = \int \mathcal{D}Y e^{-S_{\rm bias}[X,Y] - U(X_i,Y_i)/k_BT}. \quad (3)$$

where the functional $S_{\rm bias}[X,Y]$ is defined as

$$S_{\rm bias} \equiv \frac{1}{4k_BT} \int_0^t d\tau \Big[\sum_{i=1}^{N} \frac{1}{\gamma_i m_i} (m_i \ddot{\mathbf{x}}_i + m_i\gamma_i \dot{\mathbf{x}}_i + \nabla_i U - \mathbf{F}^{\rm bias}_i)^2 + \sum_{j=1}^{N'} \frac{1}{\gamma_j m_j} (m_j \ddot{\mathbf{y}}_i + m_j\gamma_j \dot{\mathbf{y}}_j + \nabla_j U)^2 \Big]. \quad (4)$$

The Onsager-Machlup functional $S_{\rm OM}[X,Y]$ entering Eq. (2) is recovered, setting $\mathbf{F}^{\rm bias}_i = 0$ in Eq. (4).

Let us now return to the problem of computing the reaction pathways in the *unbiased* Langevin dynamics [Eq. (1)]. Using the standard reweighting trick we can write the variational condition $(\delta/\delta X)\mathcal{P}[X] = 0$ as

$$\frac{\delta}{\delta X} [\mathcal{P}_{\rm bias}[X] \langle e^{-(S_{\rm OM}[X,Y] - S_{\rm bias}[X,Y,\dot{z}])} \rangle_{\rm bias}] = 0. \quad (5)$$

We now introduce our main approximation, by restricting the search for the optimum path $X(\tau)$ within an ensemble of trajectories generated by integrating the *biased* Langevin equation. By definition, these paths have a large statistical weight in the biased dynamics; i.e., they lie in the functional vicinity of some path $\bar{X}(\tau)$ which satisfies $(\delta/\delta\bar{X})\mathcal{P}[\bar{X}] = 0$. Thus, the typical biased paths approx-

This equation st that for which th force is least. In derived in the c emphasize that solvent-induced

Let us now ex history-depende the ratchet-and rithm developed in Re

formalism attempts t terms of s z. Conver spontaneo To defir (1) with a

$$-\frac{k_B}{2}\nabla$$

0

$z_m(t)$ dene time t (we obeys the Let us

$$V^R_{eff}(\mathbf{X}) \simeq \frac{D_0\,(1-b)}{\pi\, b\Omega} \nabla^2 V_{eff}(\mathbf{X}) + \frac{1}{2}\left(\frac{D_0(1-b)}{\pi\, b\Omega}\right)^2 \nabla^4 V_{eff}(\mathbf{X}) + \frac{1}{6}\left(\frac{D_0\,(1-b)}{\pi b\Omega}\right)^3 \nabla^6 V_{eff}(\mathbf{X}) - \frac{D_0^2(1-b^3)}{3\pi\,(b\Omega)^3}\left(\partial_i\partial_j V_{eff}(\mathbf{X})\right)^2. \quad (24)$$

Note that the first line is the leading order term (i.e. $L = 1$) , while the second and third lines display the order $L = 2$ and $L = 3$ corrections, respectively.

We emphasize that the result of the EST construction is a new expression for the *same* path integral (15), in which the UV cutoff been lowered from Ω to $b\Omega$. Equivalently, the path integral is discretized according to a larger elementary time step, $\Delta t \to \Delta t/b$:

$$Z^{\Delta t}(t) \equiv \oint_{\Delta t} \mathcal{D}\mathbf{X}\, e^{-S_{eff}[\mathbf{X}]} \propto \oint_{\Delta t/b} \mathcal{D}\mathbf{X}\, e^{-S_{eff}[\mathbf{X}] - \int_0^t d\tau\, V^R_{eff}[\mathbf{X}(\tau)]} \equiv Z^{\Delta t/b}_{EST}(t) \quad (25)$$

In these expressions, the symbol $\oint_{\Delta t}$ denotes the fact that the path integral is discretized according to an elementary time step Δt and we have suppressed the subscript "<", in the paths. It can be shown that the proportionality factor between $Z^{\Delta t}(t)$ and

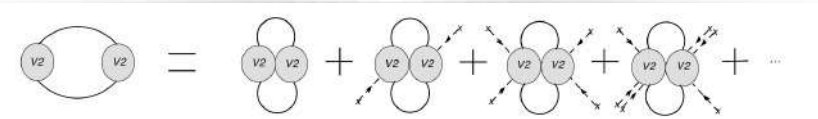


FIG. 3: Diagrammatic representation of the local time-derivative expansion of a non-local diagram —Eq. (49)—. Solid lines are fast-mode propagators, while dashed lines represent a single time derivative acting on the corresponding vertex function.

Notice that each term in the perturbative expansion (35) generates a new vertex, with an increasing power of the $x_>(\tau)$ field. The couplings to the fast modes depend implicitly on the time τ, through the slow modes $x_<(\tau)$.

By Wick theorem, each term in the series (34) can be related to a Feynman graph with vertexes given by (36) and propagators given by —see appendix A —:

$$\langle x^i_>(\tau_1)\; x^j_>(\tau_2)\rangle_0 = \sum_{|\omega_m|,|\omega_n| \in S_b} G^{0\;ij}_>(\omega_n, \omega_m)\; e^{i(\omega_m\tau_1 + \omega_n\tau_2)} = \sum_{|\omega_n| \in S_b} \delta_{i,j}\, \frac{2}{\beta\,\gamma\; t\;\omega_n^2}\, e^{i\omega_m(\tau_2 - \tau_1)}. \quad (37)$$

The expansion (34) can be re-organized as the exponent of the sum performed over only connected diagrams:

$$e^{-\beta\; S_>[x<(\tau)]} = e^{\sum \{\text{all connected diagrams}\}}. \quad (38)$$

Hence, the path integral (26) for the slow modes can be given the following exact diagrammatic representation

$$Z(t) \equiv \oint \mathcal{D}x_<\; e^{-\beta\; S_{eff}[x_<(t)]] + \sum \{\text{all connected diagrams}\}}. \quad (39)$$

Below we give a classification of all the connected diagrams that may give a contribution to the expansion above

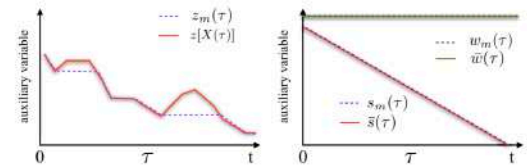


FIG. 1. Illustrative representation of the dynamics of the auxiliary variables introduced in the path integral representation of rMD (left panel) and in the derivation self-consistent path sampling algorithm (right panel).

of such a variable is frozen any time z_m becomes smaller than $z(X)$ and any time the collective coordinate $z(X)$ is increasing. Its time derivative is otherwise set equal to $\dot{z}(X)$. Therefore, by choosing the initial conditions $z_m(0) = z(X(0))$, $z_m(\tau)$ is identically set equal to the minimum value attained by the collective coordinate z until time τ (see left panel of Fig. 1).

The functional $S_{rMD}[X, z_m]$ in the exponent of Eq. (8) coincides with an OM action with the addition of the unphysical biasing force $\mathbf{F}_i$.

$$S_{rMD} = \sum_{i=1}^{N} \Gamma_i \int_0^t d\tau \left[m_i\ddot{\mathbf{x}}_i + m_i\gamma_i\dot{\mathbf{x}}_i + \nabla_i U - \mathbf{F}_i\right]^2. \quad (9)$$

In Eq. (8), $\Phi[z_m, X]$ denotes a Jacobian factor that needs to be introduced in order to ensure that the statistical weight of the paths is not affected by the measure of the $\int \mathcal{D}z_m$ integral, i.e.,

$$\int \mathcal{D}z_m \Phi[z_m, X]\; \delta\left[z_m(\tau) - \int_0^\tau d\tau' \dot{z}[X(\tau')]\theta(-\dot{z}[X(\tau')])\right.$$

III. SELF-CONSISTENT PATH SAMPLING

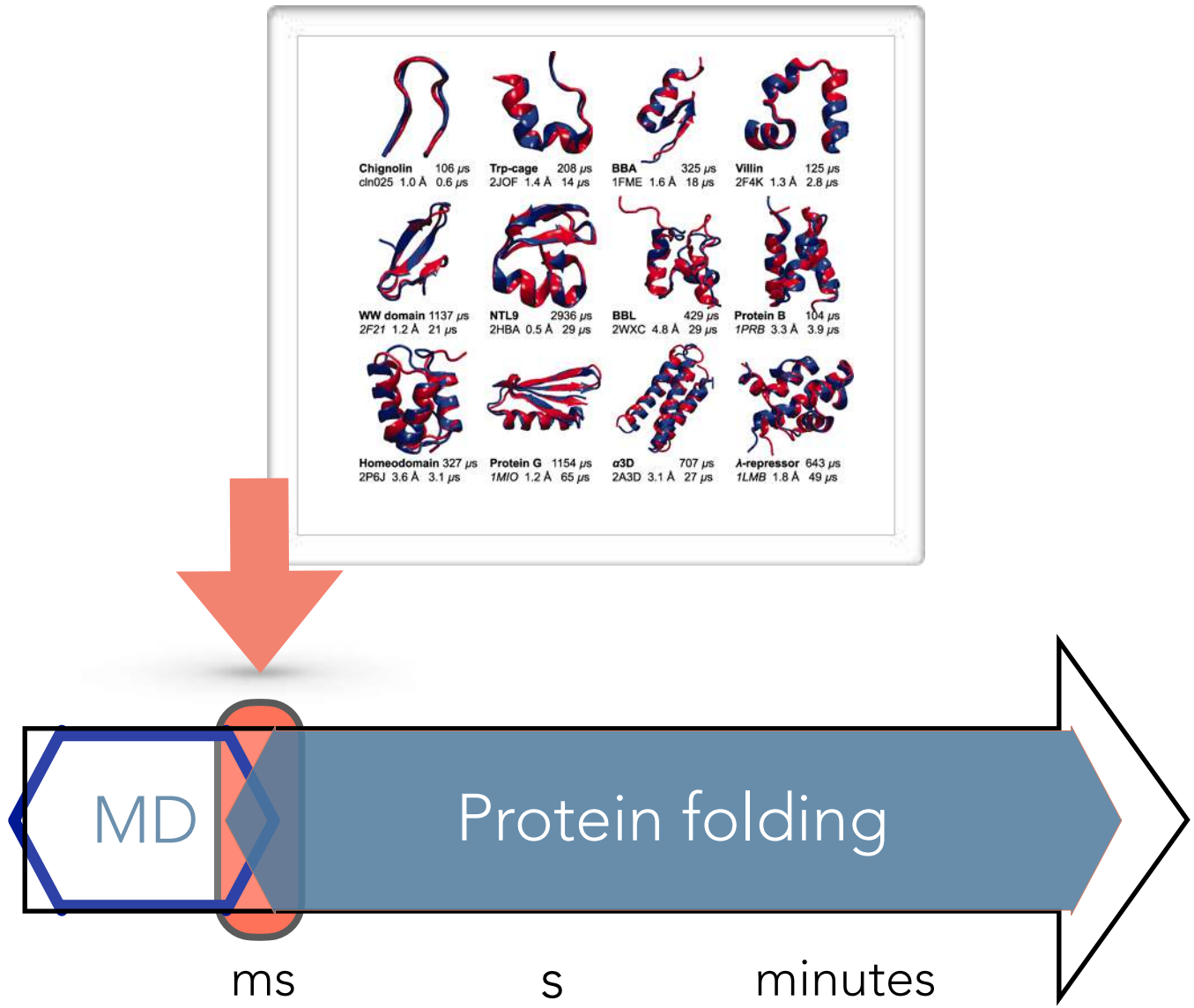
Let us now introduce our new algorithm, which provides major improvement with respect to the rMD and BF schemes discussed in Sec. II A. Indeed, it follows directly from the unbiased Langevin equation and allows us to remove the systematic errors associated to the choice of biasing coordinate.

Our starting point is path integral representation of the *unbiased* Langevin dynamics (2). We introduce two dumb auxiliary variables $w_m(\tau)$ and $s_m(\tau)$ into this path integral by means of appropriate functional Dirac deltas,

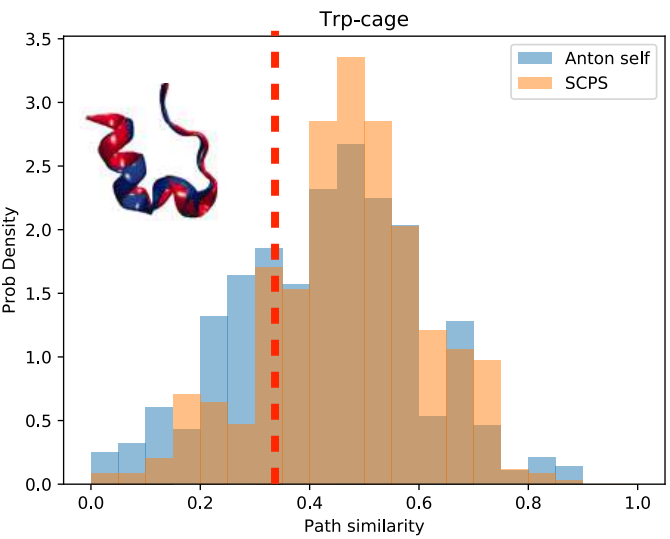
$$p(X_N, t|X_U) = \int_{X_U}^{X_N} \mathcal{D}X \cdot e^{-S[X]} \int_{\mathbb{R}(0)} \mathcal{D}s_m \int_{\bar{w}(0)} \mathcal{D}w_m \cdot \delta\left[w_m(\tau) - \int_0^\tau d\tau' \hat{w}(\tau')\,\theta(-\hat{w}(\tau'))\,\theta(w_m(\tau') - \bar{w}(\tau'))\right] \cdot \delta\left[s_m(\tau) - \int_0^\tau d\tau' \hat{s}(\tau')\,\theta(-\hat{s}(\tau'))\,\theta(s_m(\tau') - \bar{s}(\tau'))\right], \quad (12)$$

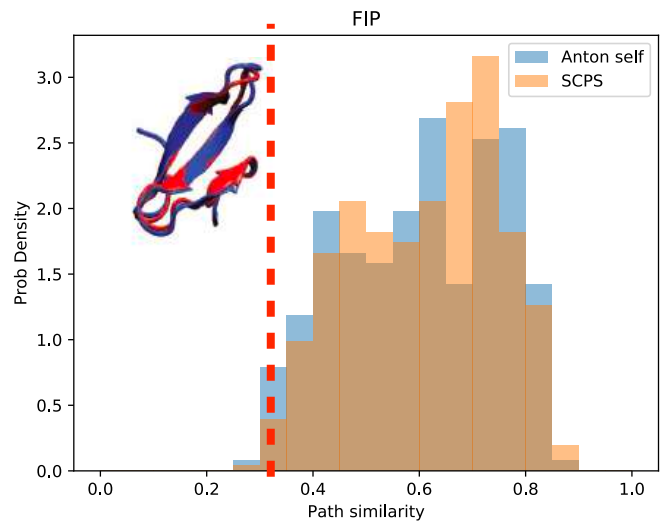
where $\bar{s}(\tau)$ and $\bar{w}(\tau)$ are two external time-dependent functions to be defined below. In analogy with the path integral repre-

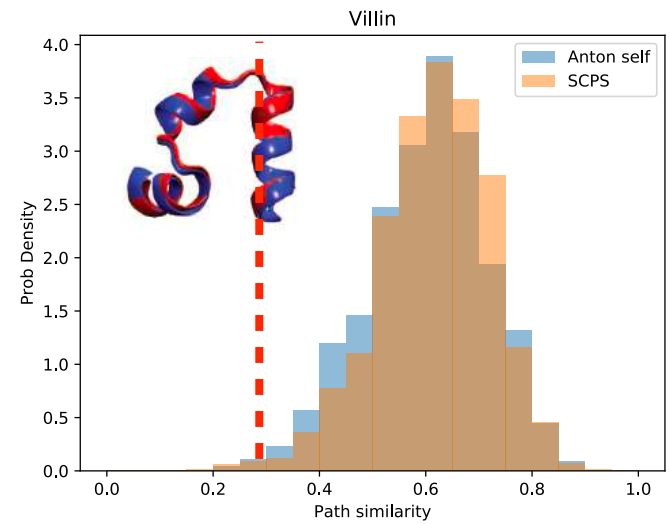
VALIDATING SCPS AGAINST MD

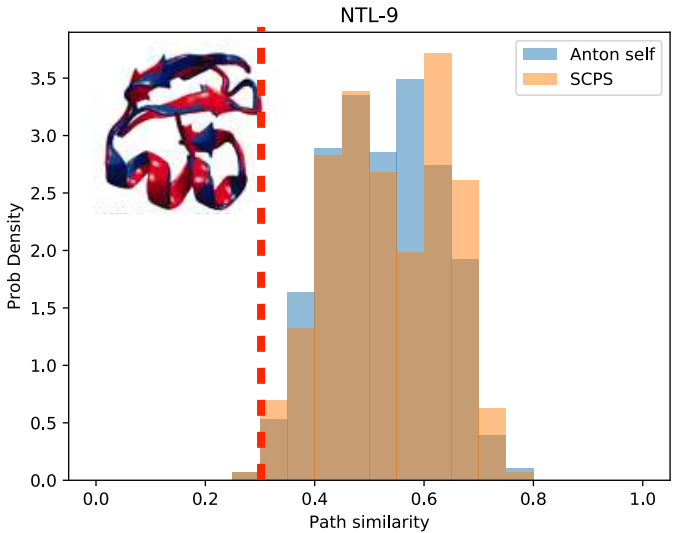


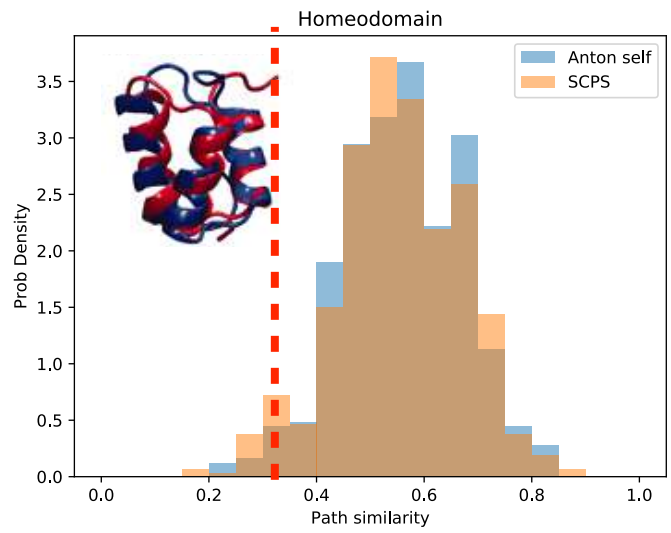
VALIDATING SCPS AGAINST MD

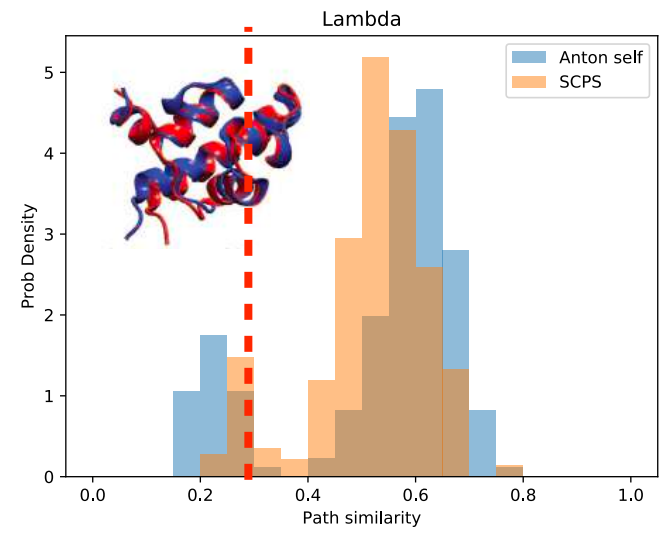




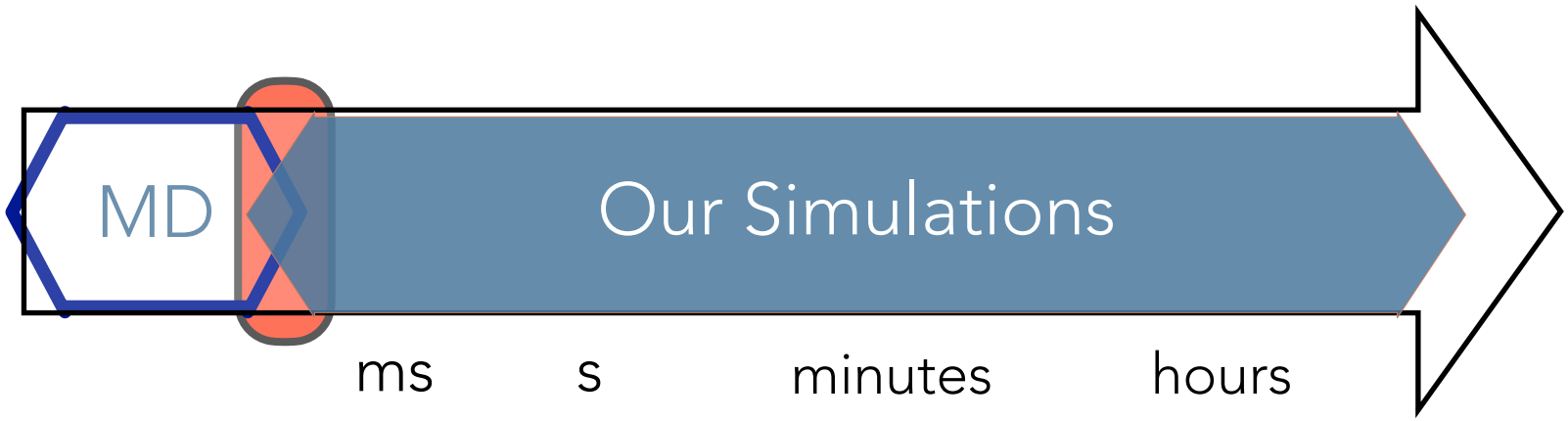


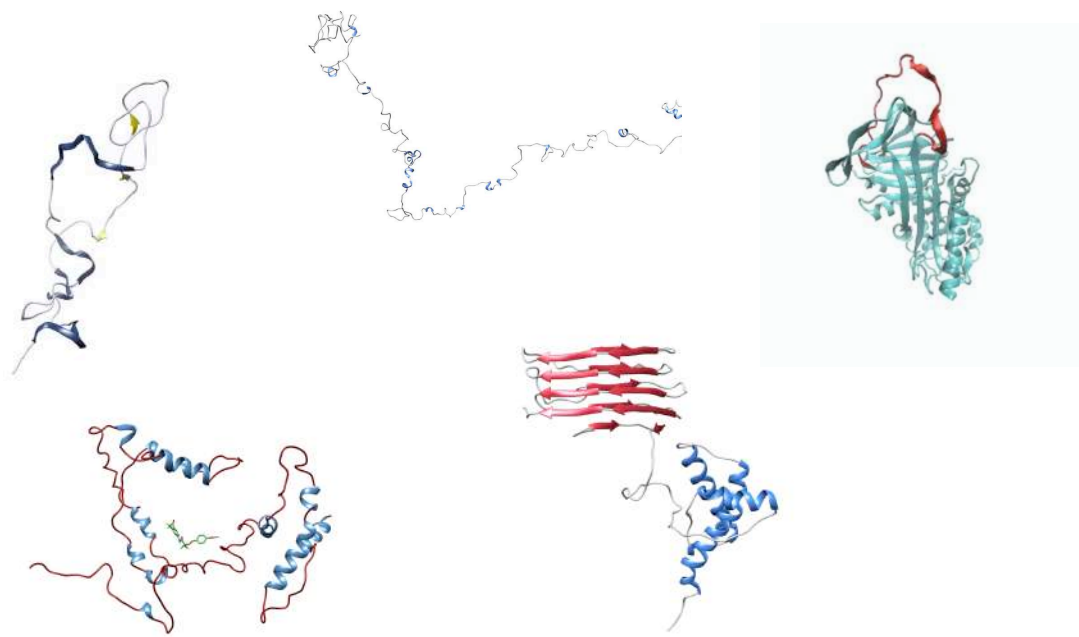




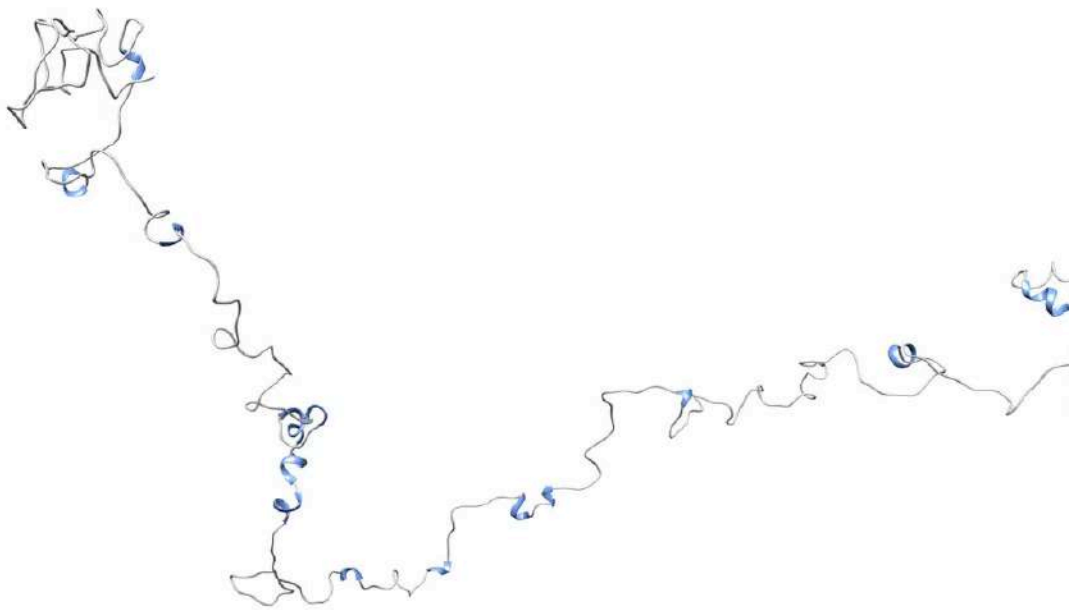


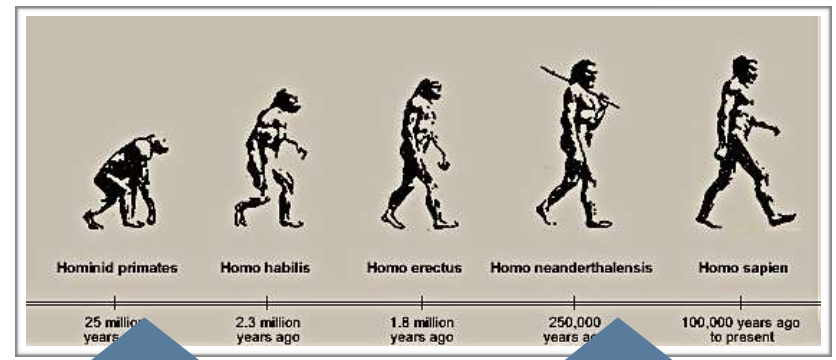
VENTURING INTO THE BIO-ZONE





HUGE COMPUTATIONAL GAIN

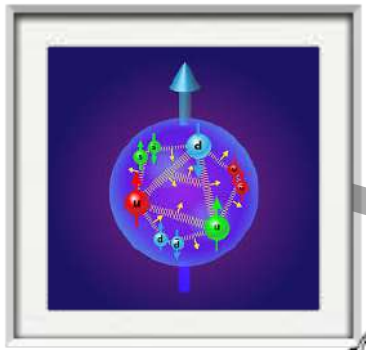


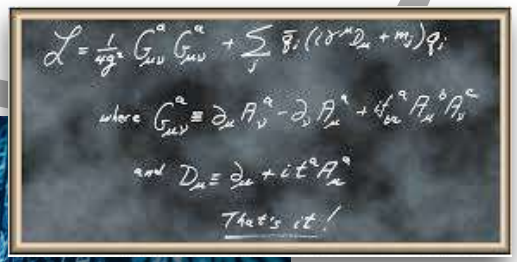


Using top all-purpose supercomputers

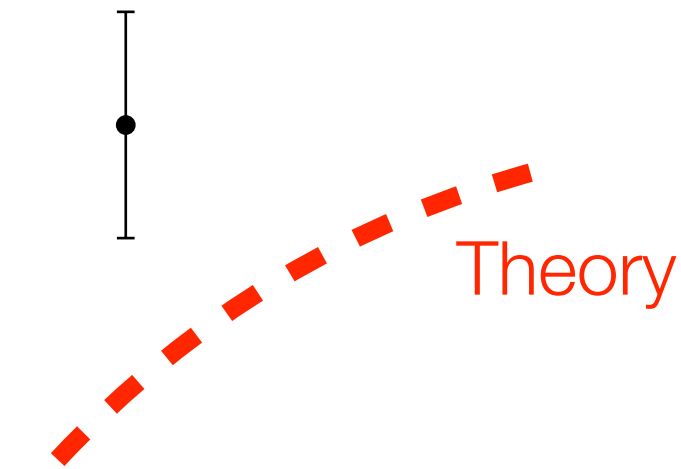
Using top special-purpose supercomputer

PHASE 2: VALIDATION





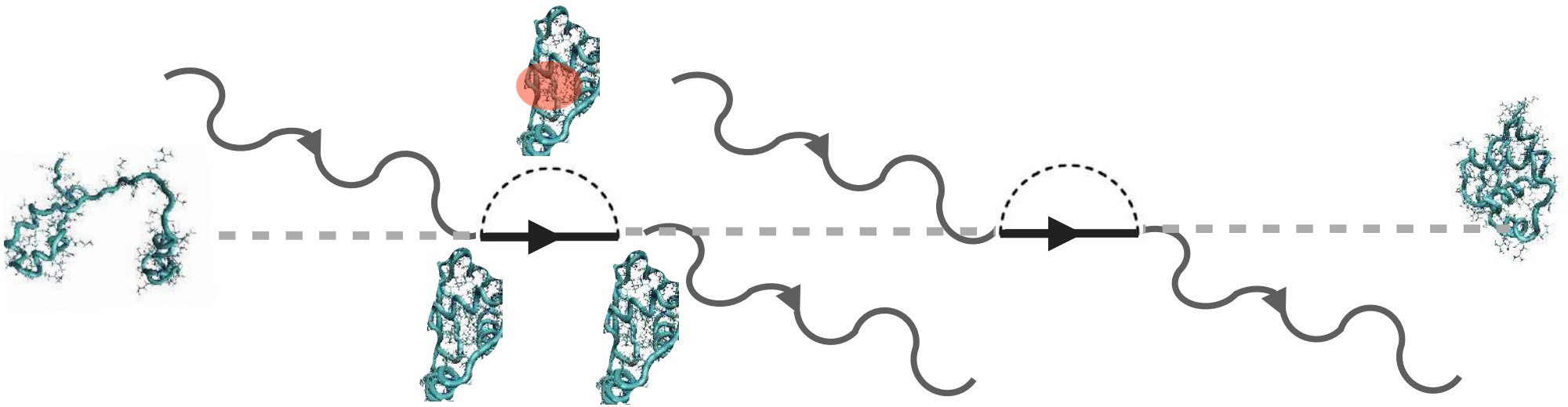
VALIDATION AGAINST EXPERIMENT



Challenge:

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

TIME-DEPENDENT LINEAR SPECTROSCOPY



Ground state

One exciton

Challenge:

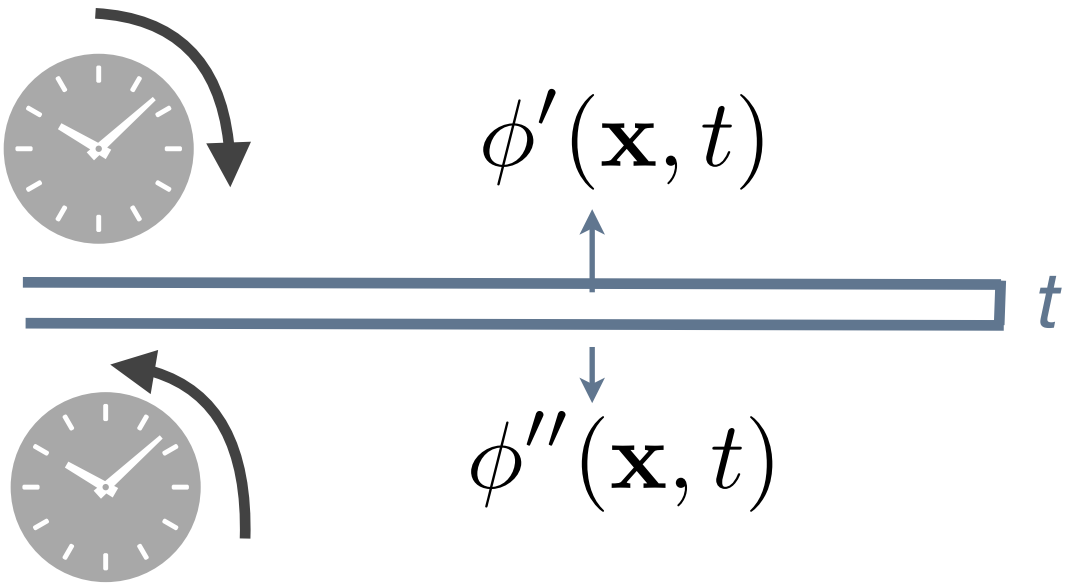
Need a theory for **non-equilibrium dynamics** of **quantum** electronic excitations in conformationally evolving proteins

$$\hat{\rho}(t) = e^{\frac{i}{\hbar}\hat{H}t}\ \hat{\rho}(0)\ e^{-\frac{i}{\hbar}\hat{H}t}$$

multiple time directions…

USE QUANTUM FIELD THEORY!

Using QFT we get rid of the multiple time issue:



$$\psi = \begin{pmatrix} \phi' \\ \phi'' \end{pmatrix}$$

Just like
anti-particles

One “relativistic” field doublet but just one time

MOLECULAR QUANTUM FIELD THEORY*

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

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

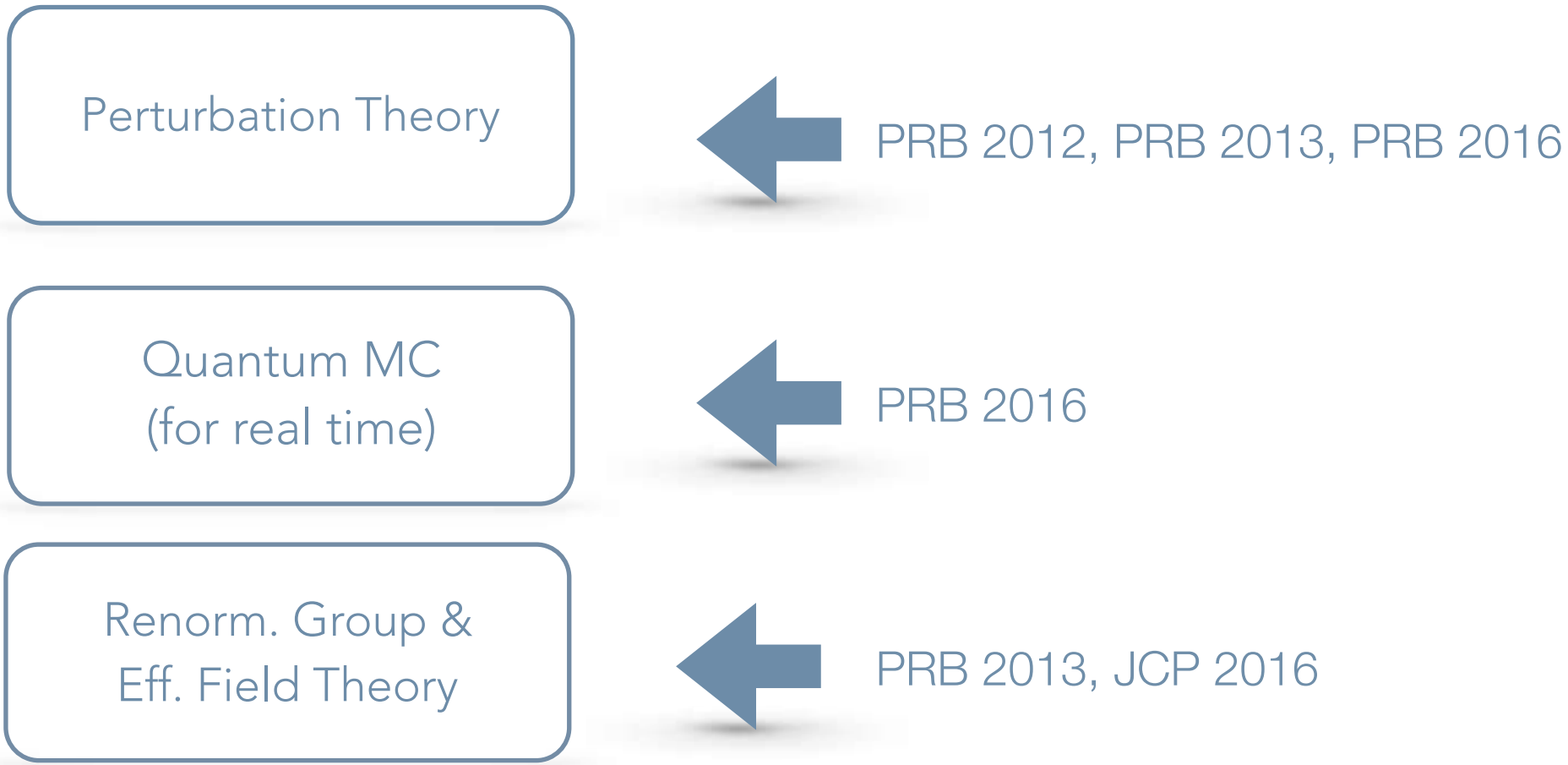
$$S_{OM}[q] = \int_0^t d\tau \frac{\beta}{4M\gamma} \left(M\ddot{q} + M\gamma\dot{q} + \nabla U(q)\right)^2$$

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

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

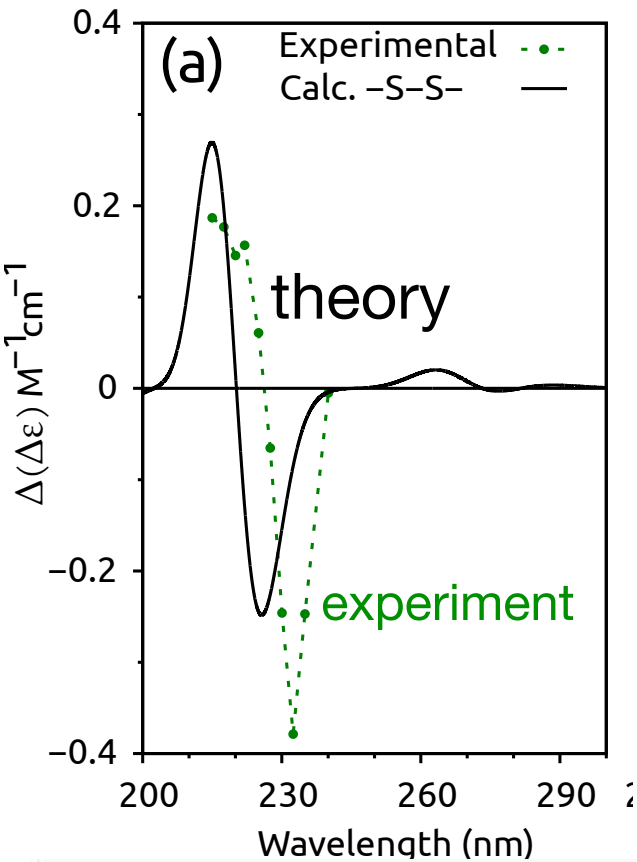
P. Faccioli & E. Schneider (2013-2016)

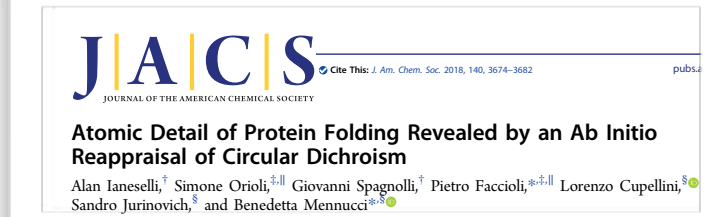
SOLVING MQFT: AN ARSENAL OF METHODS



EXAMPLES OF DIRECT COMPARISON WITH EXPERIMENTS

Time resolved near UV CD*





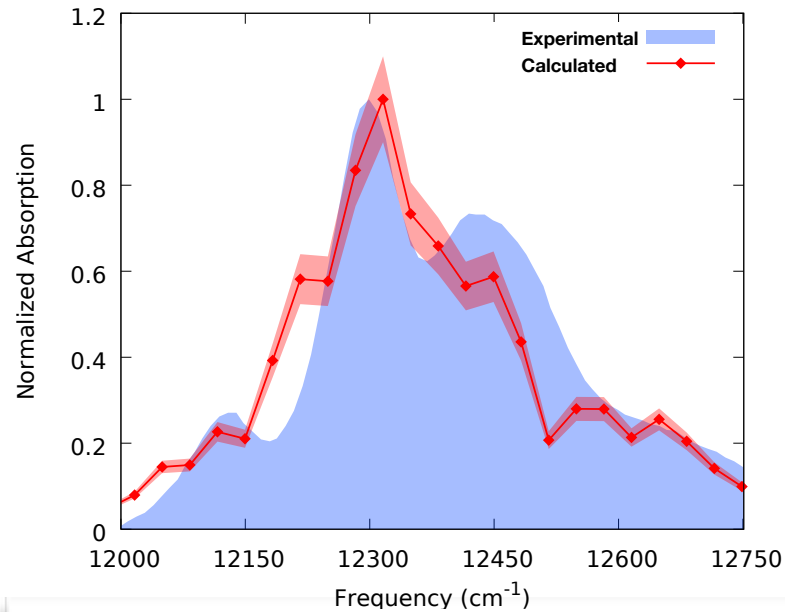
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

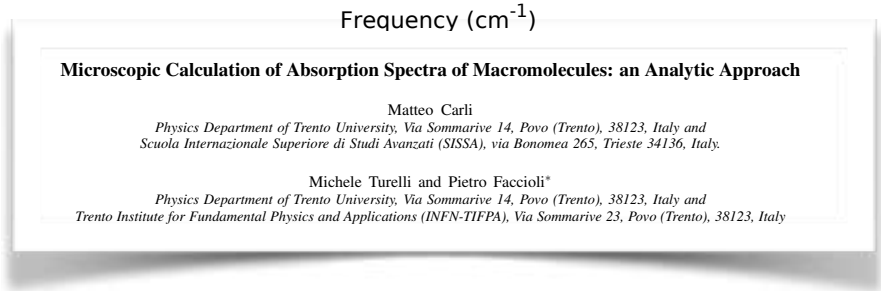
Cite This: J. Am. Chem. Soc. 2018, 140, 3674–3682

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





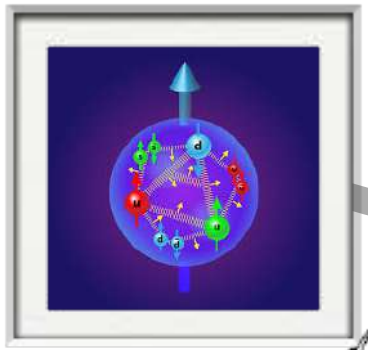
Microscopic Calculation of Absorption Spectra of Macromolecules: an Analytic Approach

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

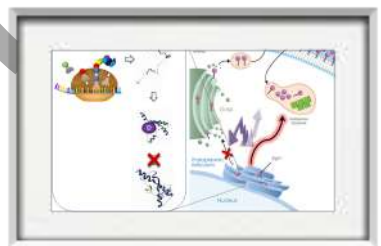
* with B. Mennucci's Lab (U. Pisa)

PHASE 3: EXPLOITATION IN MOLECULAR BIOLOGY

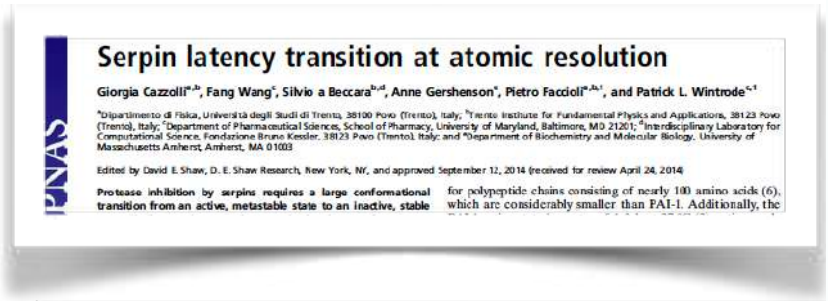


Experiment

Theory



EXPLORING BIOLOGICAL PROCESSES



PNAS

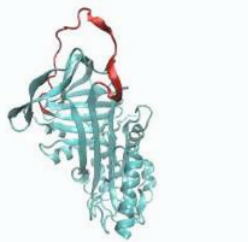
Serpin latency transition at atomic resolution

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

[a]Dipartimento di Fisika, 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 FAI-1. Additionally, the



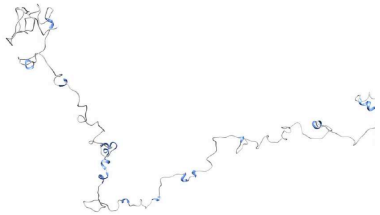
Biophysical Journal

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,*]

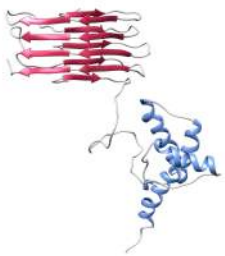


PLOS | PATHOGENS

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]*



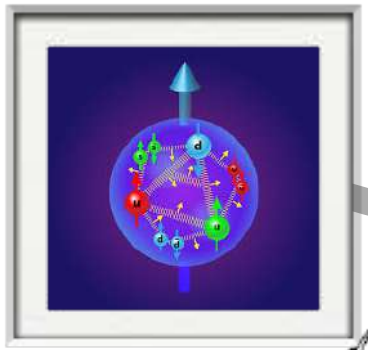
All-Atom Simulation of the HET-s Prion Replication

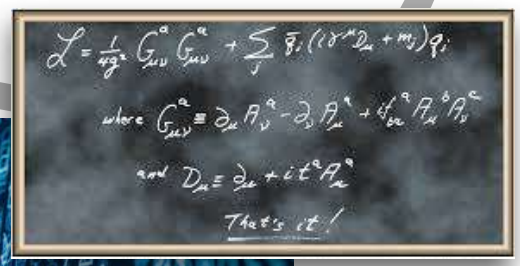
Luca Terruzzi[1,2]*, Giovanni Spagnolli[2,3]*#, Alberto Boldrini[1,2], Jesús R. Requena[4], Emiliano Biasini[2,3]# and Pietro Faccioli[5,6]#

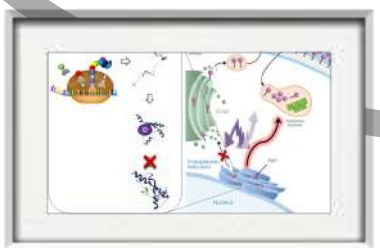
Teaming up with

E. Biasini's lab (DICIBIO)

PHASE 4: PHARMACOLOGICAL RESEARCH







ROLE OF PROTEIN INACTIVATION

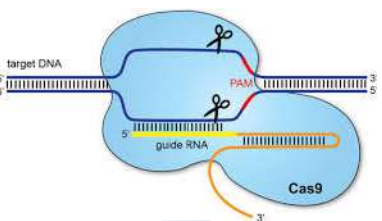
MOST OF BIOLOGICAL FUNCTIONS IN CELLS ARE CARRIED OUT BY **PROTEINS**

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

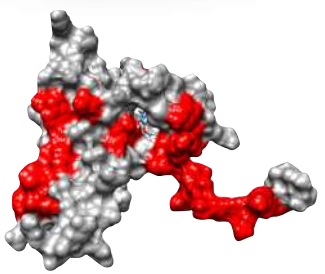
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING

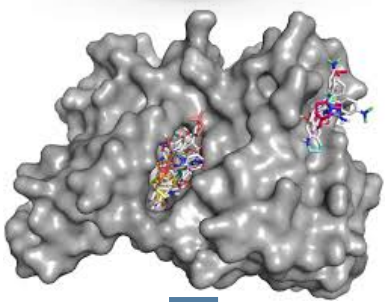
patent file # 102018000007535 (with E. Biasini)

DNA → mRNA → Ribosome → Protein folding → Protein function



RNA silencing





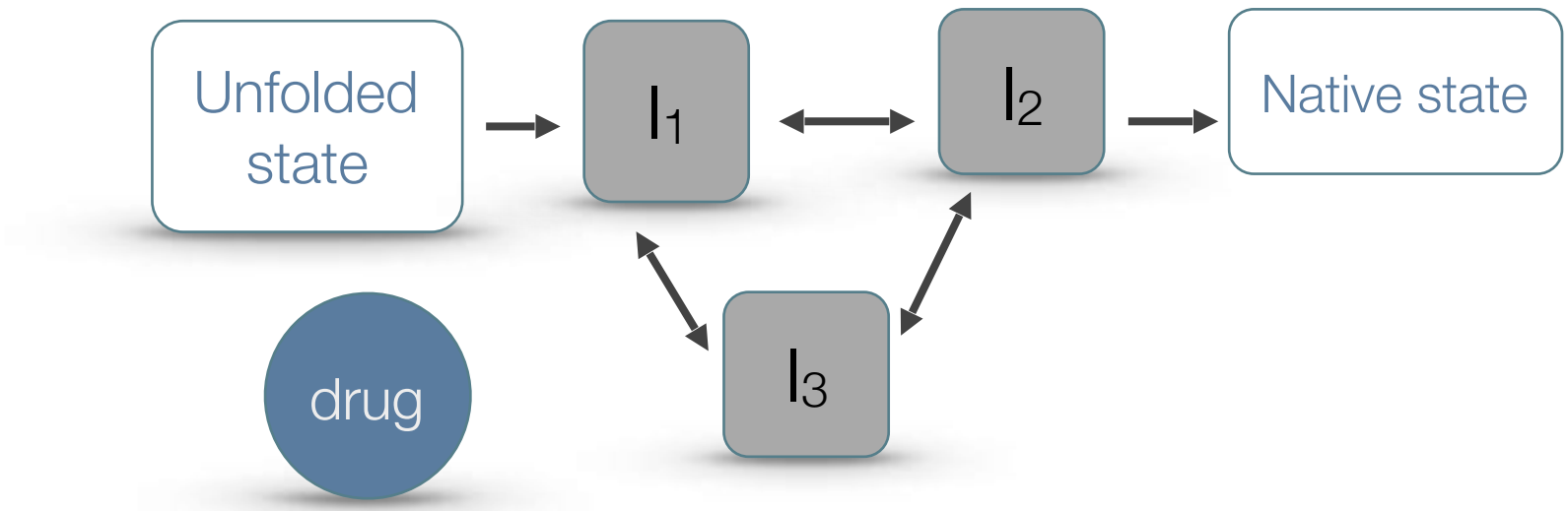
Eliminating protein from genome

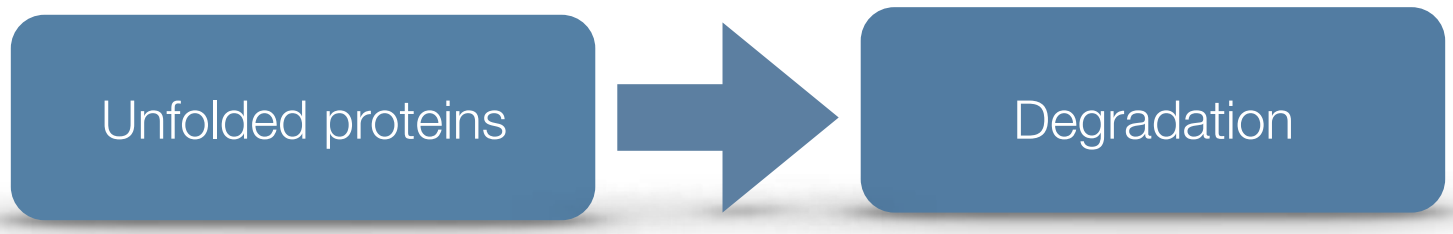
Suppressing transcription

Suppressing folding

Imparing function

PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING



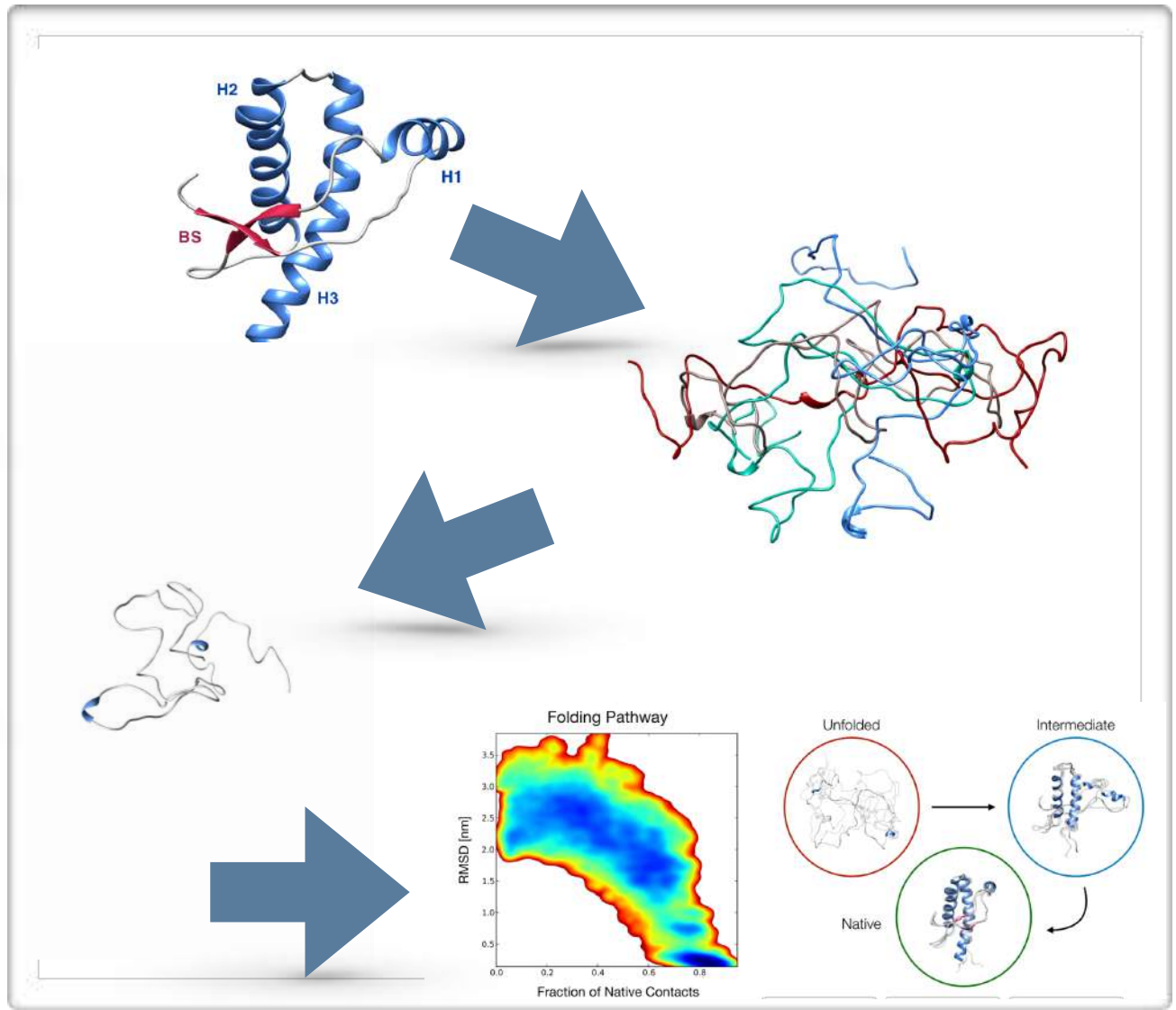


PPI-FIT PIPELINE

Folding pathway characterization

Virtual screening on folding Intermediate

Biochemical Validation



PPI-FIT PIPELINE

Folding pathway characterization

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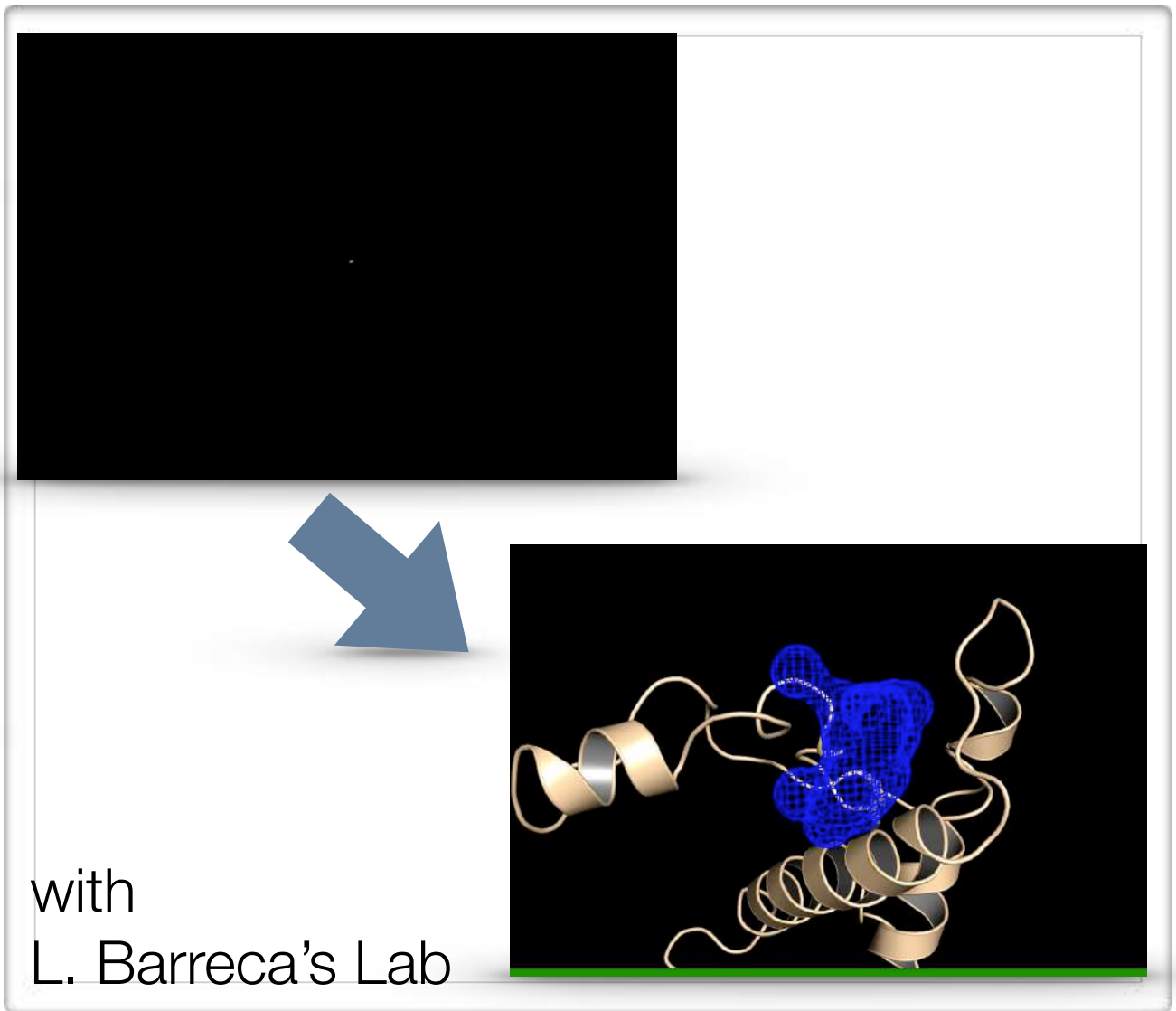
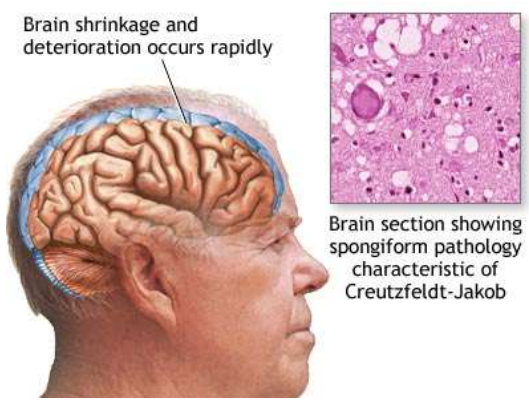


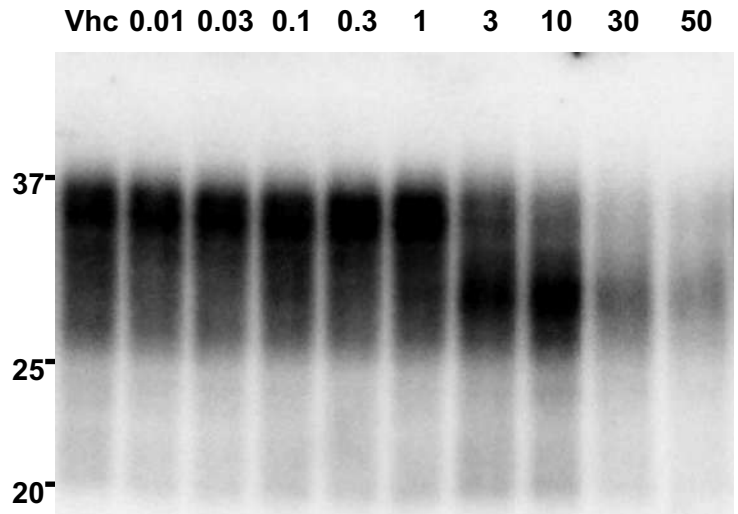
with
L. Barreca's Lab

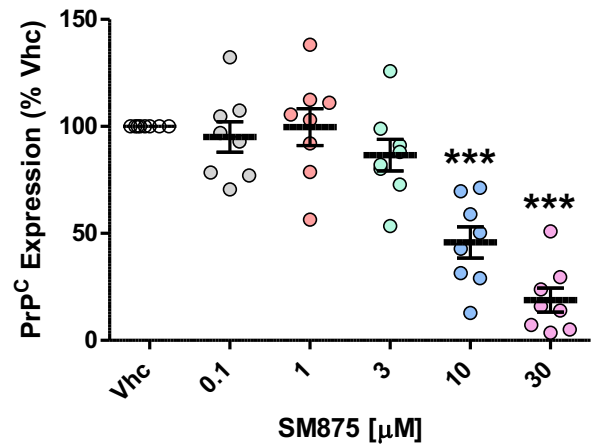
DRUGGING THE UNDRUGGABLE

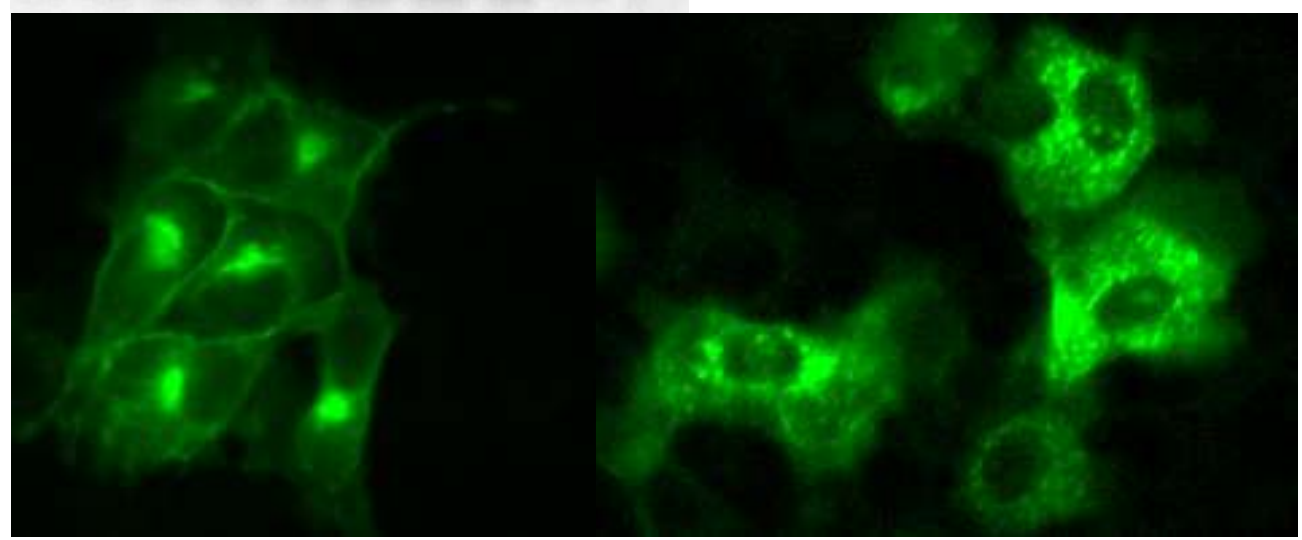
Inactivation of Cellular Prion protein



Brain section showing spongiform pathology characteristic of Creutzfeldt-Jakob







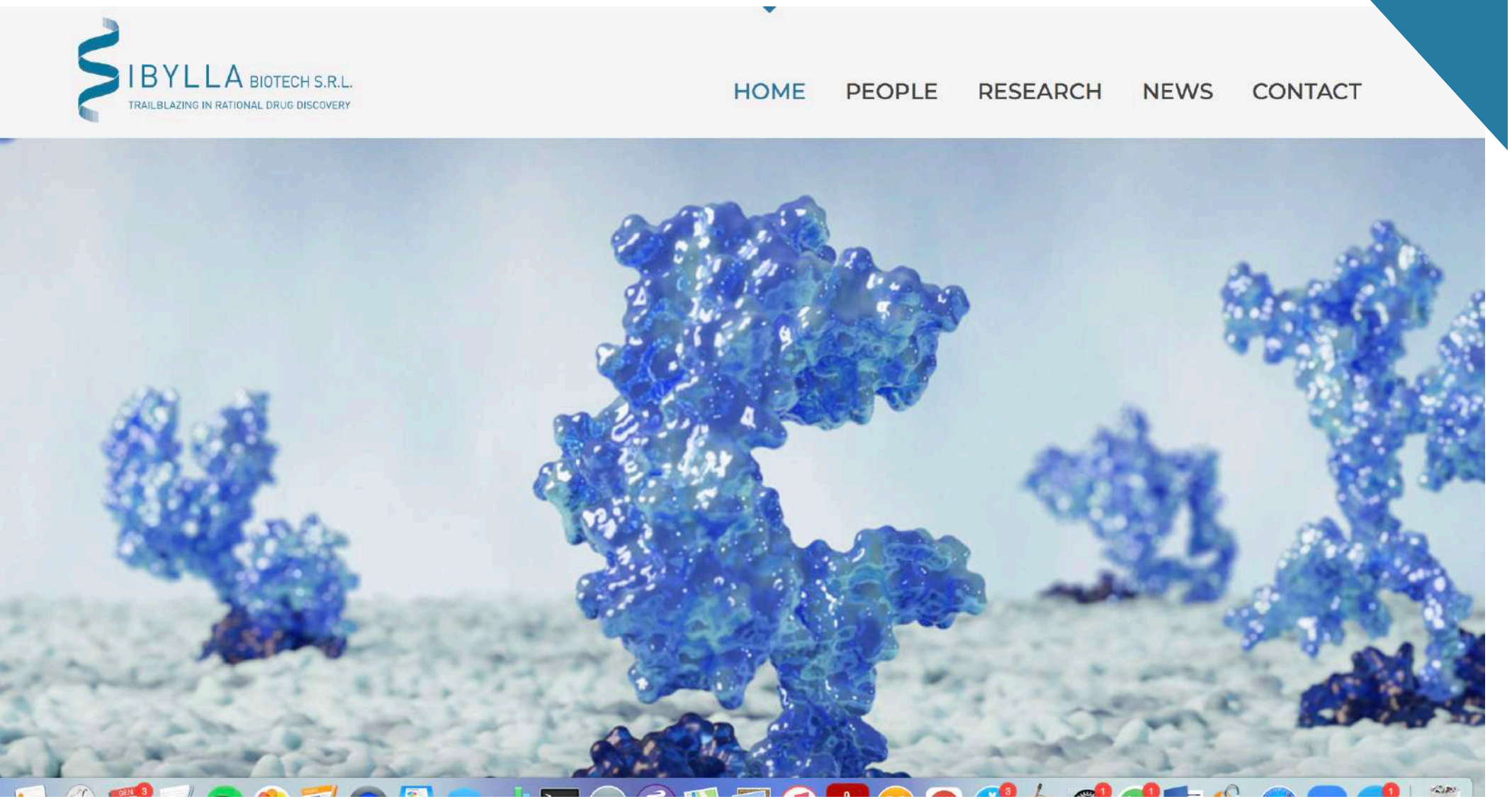
COMMUNICATIONS BIOLOGY

ARTICLE

https://doi.org/10.1038/s42003-020-01585-x OPEN

Pharmacological inactivation of the prion protein by targeting a folding intermediate

Technology Transfer Initiative



Joining Forces against **COVID-19**

Maria Letizia Barreca

UNIVERSITÀ DEGLI STUDI DI PERUGIA

Emiliano Biasini

UNIVERSITÀ DI TRENTO

FONDAZIONE Telethon

Pietro Faccioli

UNIVERSITÀ DI TRENTO

TIFPA

Graziano Lolli

UNIVERSITÀ DI TRENTO

INFN

Istituto Nazionale di Fisica Nucleare

30.000 cores in 8 data centers

Lidia Pieri

Giovanni Spagnolli

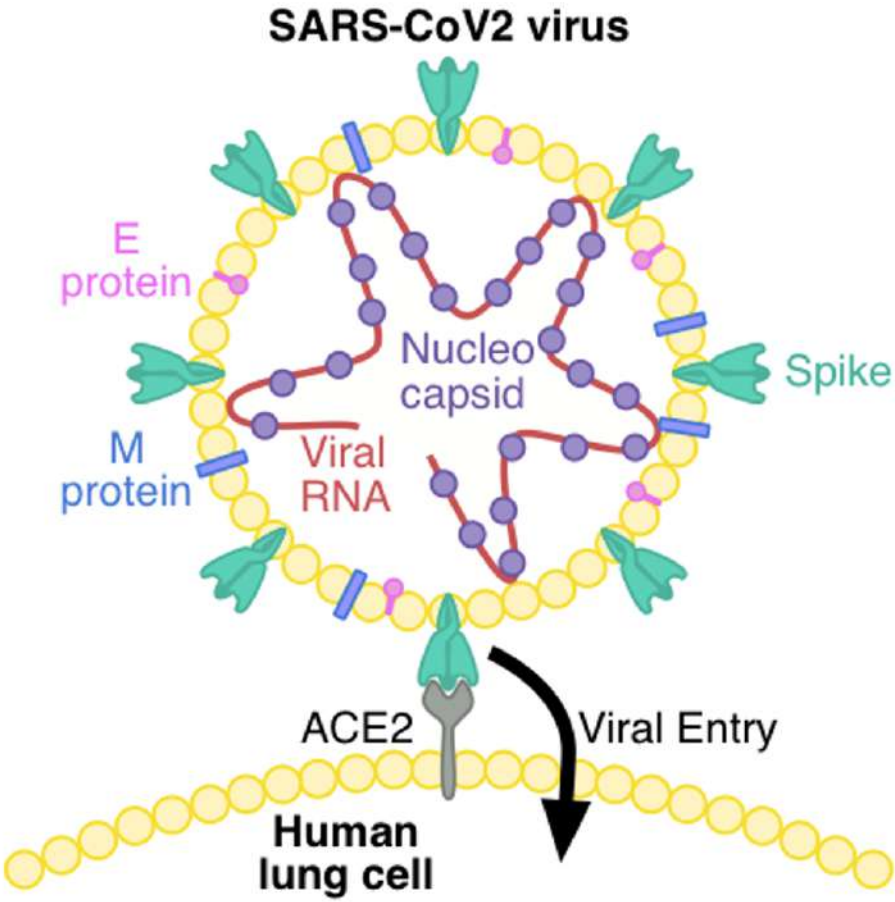
Alberto Boldrini

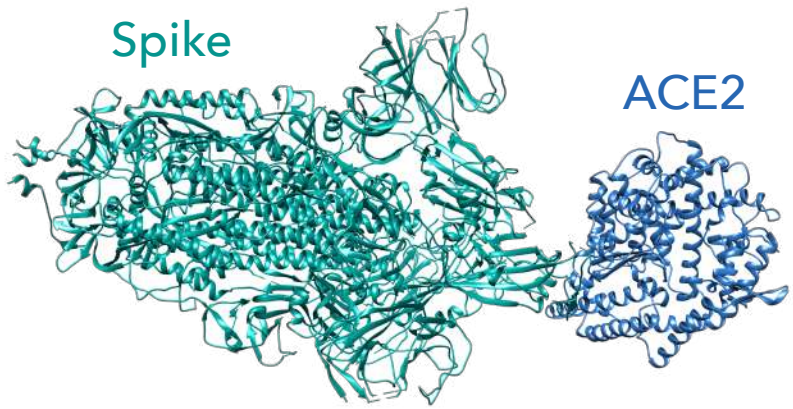
Tania Massignan

Luca Terruzzi

Andrea Astolfi

SARS-CoV-2 Replication





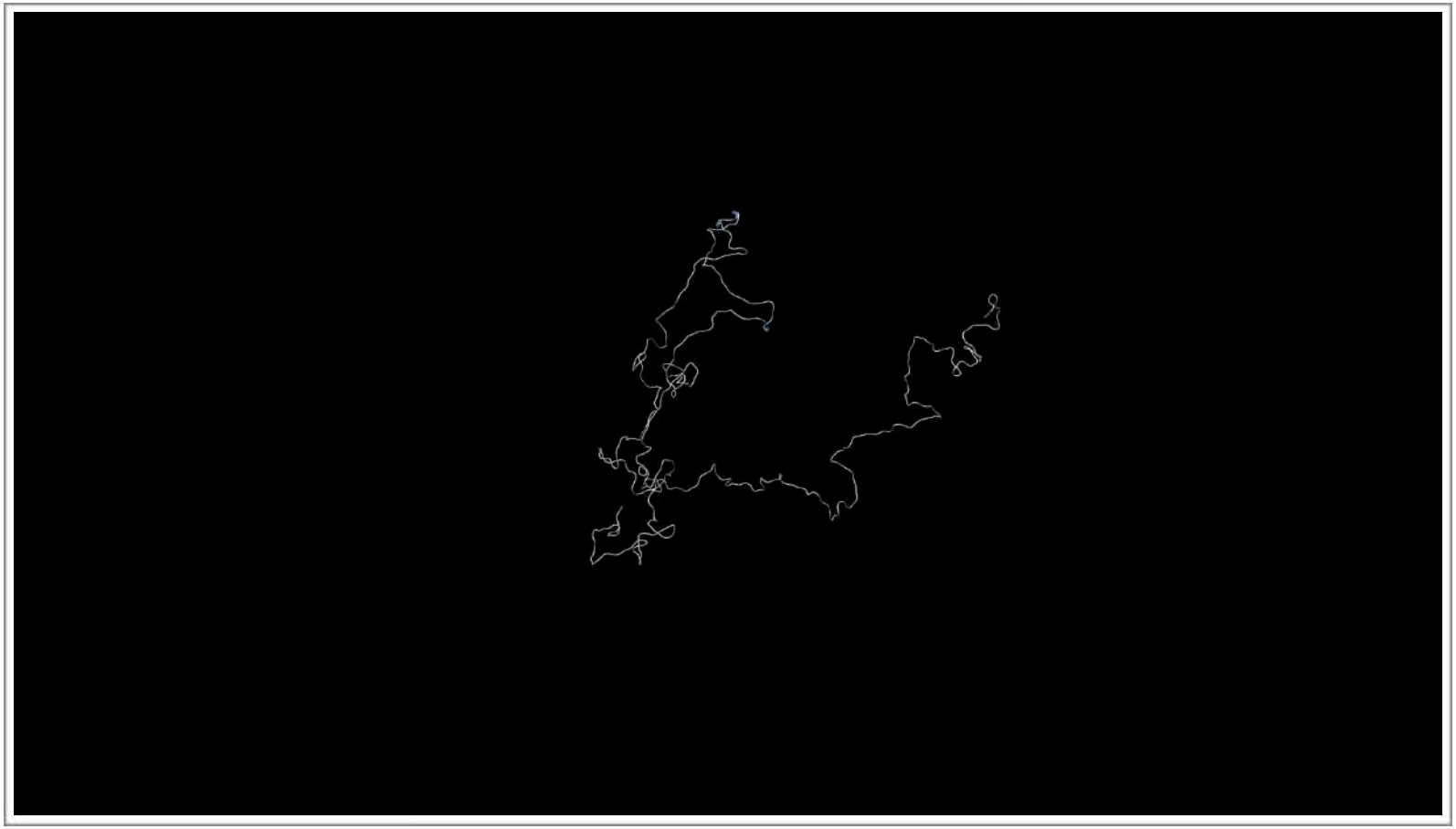
Goals:

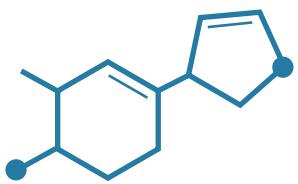
Repurposing of approved drugs!

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

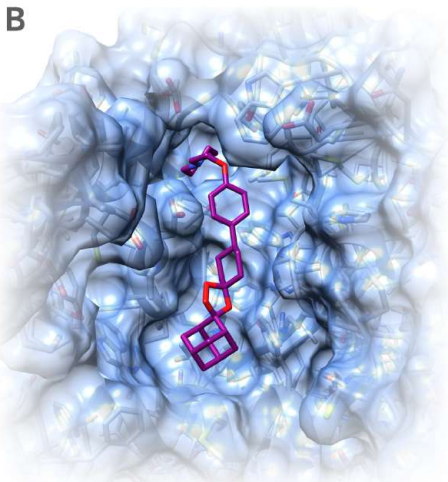


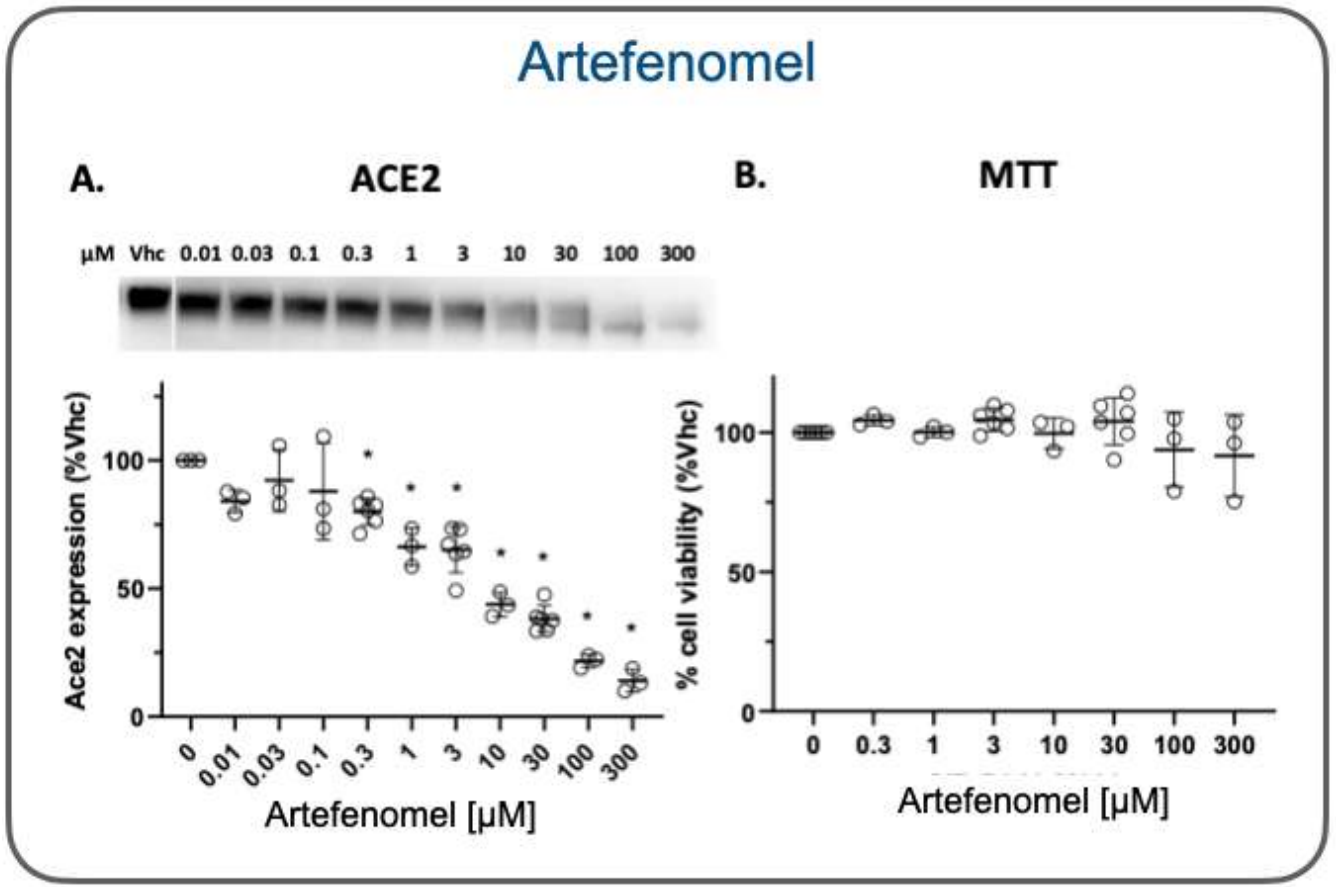


Out of 9000 candidates, we found 35 molecules binding in-silico the intermediate. Validation experiments on cellular bio-assays are ongoing.

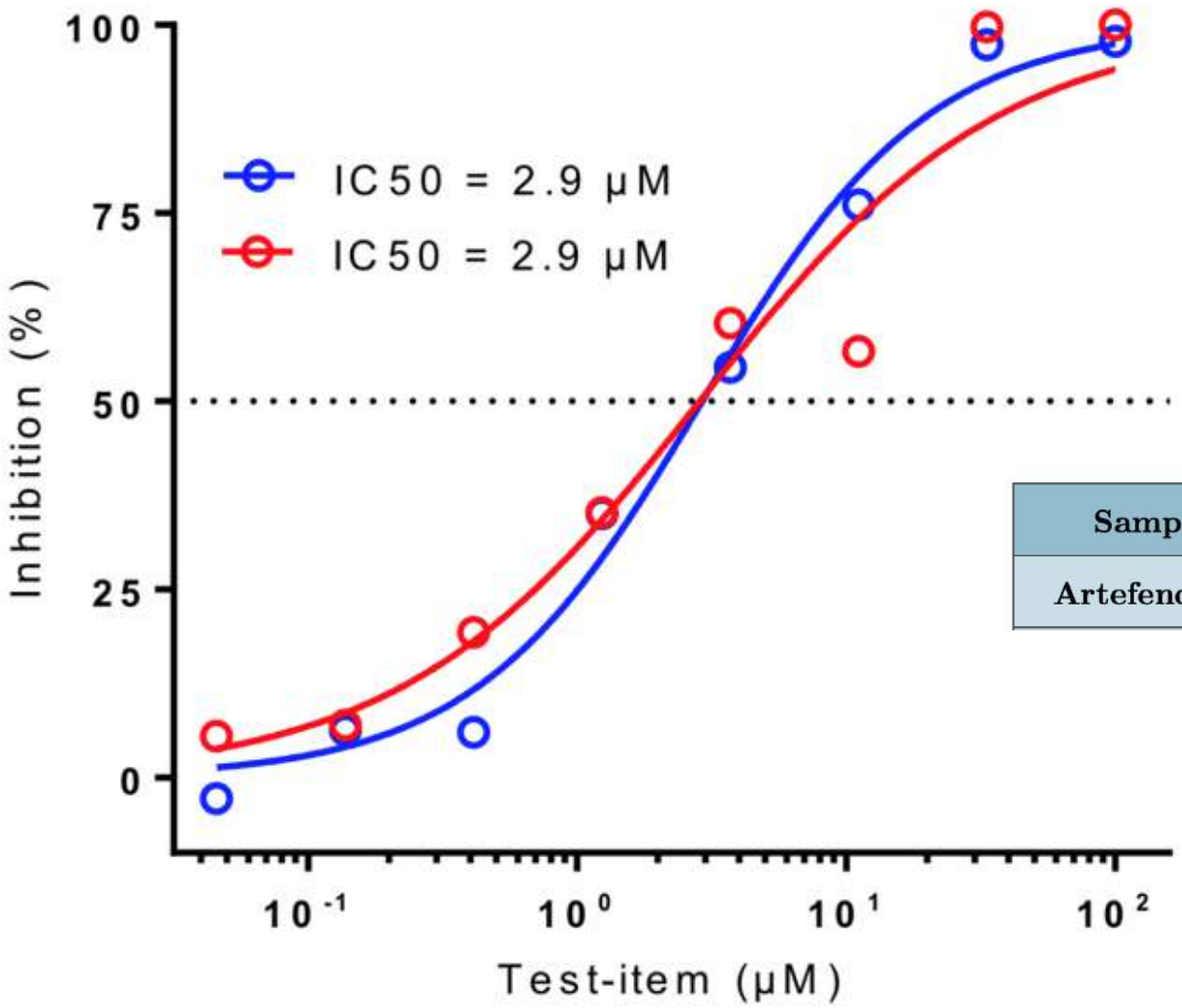
DOSE-DEPENDENT RESPONSE

B





ANTI-VIRAL ACTIVITY AGAINST LIVE SARS-COV2



Concentration at which it becomes active

Sample	IC50 [µM]	CC50 [µM]
Artefenomel	2.9	> 100

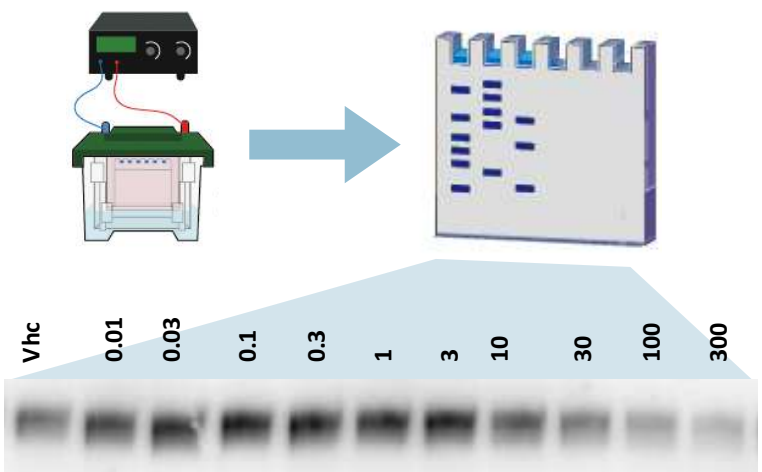
Concentration at which it becomes toxic

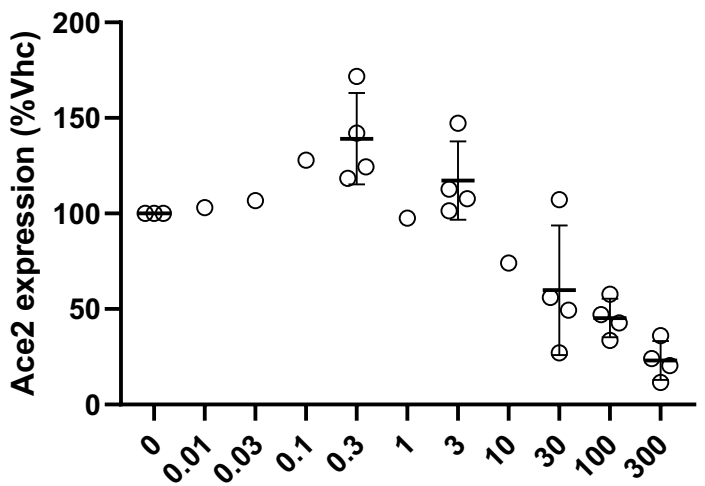
This value is *in principle* compatible with the maximum tolerated dose in humans. More to follow…

BREAKING NEWS!! (17/05/2020)

So far, Sibylla Biotech has tested 14 virtual hits

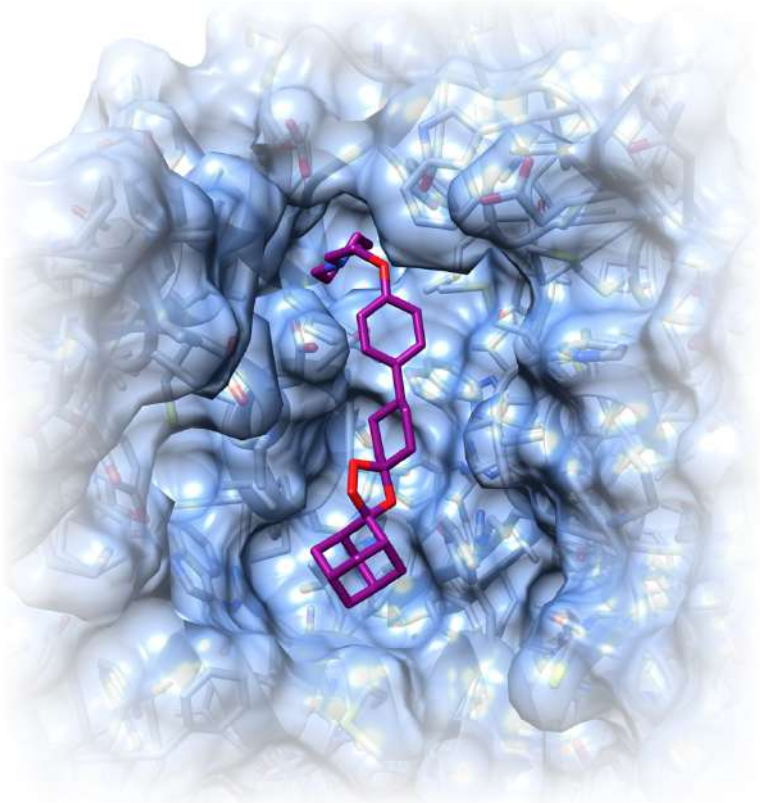
ONE DISPLAYS A **PROMINENT EFFECT** WITH CLEAR **DOSE-RESPONSE** RELATIONSHIP AND VERY **LOW TOXICITY**





SPACE IS THE NEXT FRONTIER!

A MAIN LIMITING FACTOR



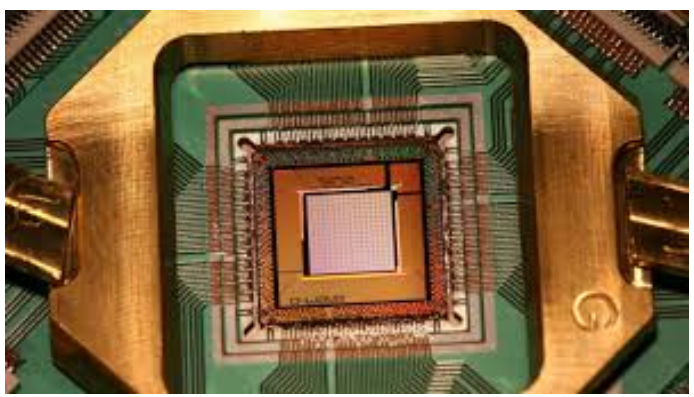
Impossible to crystallize
folding intermediates
on Earth

Microgravity conditions may provide the solution!

Molecular Biology PRIN
(functional role of folding intermediates?)

ZEFIR MISSION*

Quantum Computing + AI



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Dominant Reaction Pathways by Quantum Computing

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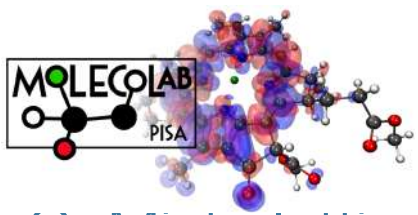

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