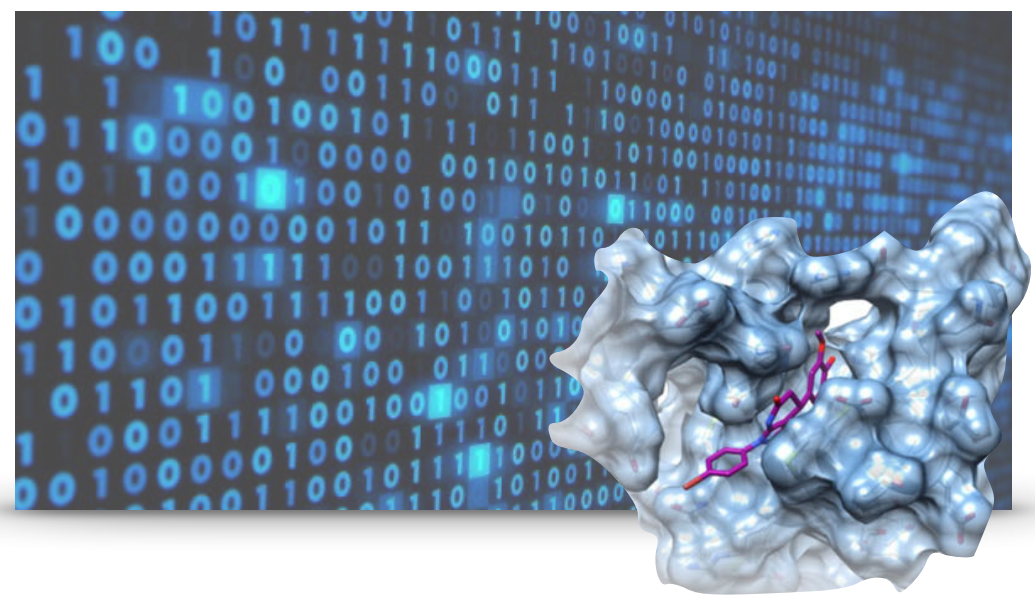
Can Theoretical Physics Help Develop New Therapeutic Strategies?

Pietro Faccioli

Trento University & INFN



THREE PIVOTAL QUESTIONS FOR THIS TALK

Can mathematical methods of high-energy physics be harnessed to address biologically relevant questions?

Can we generate new insight to envision new therapeutic strategies?

What do emerging technologies have to offer?

THREE PIVOTAL QUESTIONS FOR THIS TALK

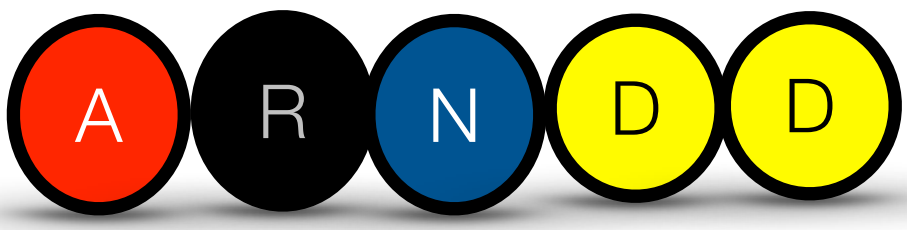
Can mathematical methods of high-energy physics be harnessed to address biologically relevant questions?

Can we generate new insight to envision new therapeutic strategies?

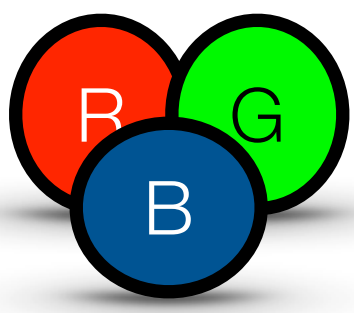
What do emerging technologies have to offer?

PROTEINS vs HADRONS

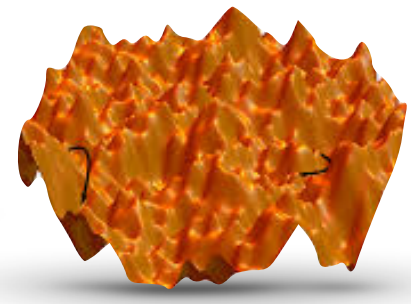
Random polypeptide

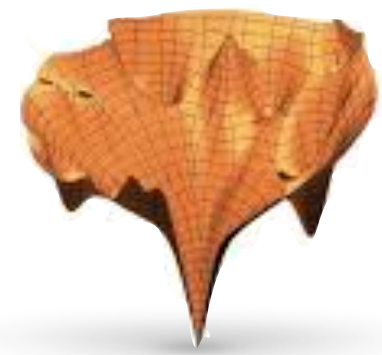


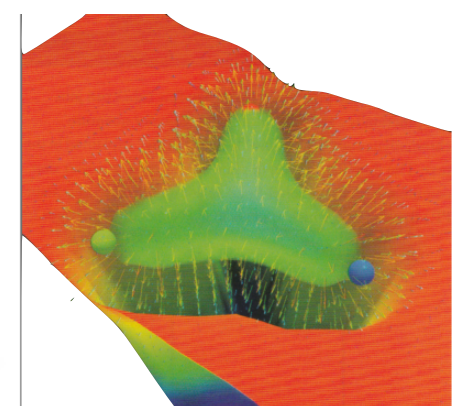
Protein



Baryon

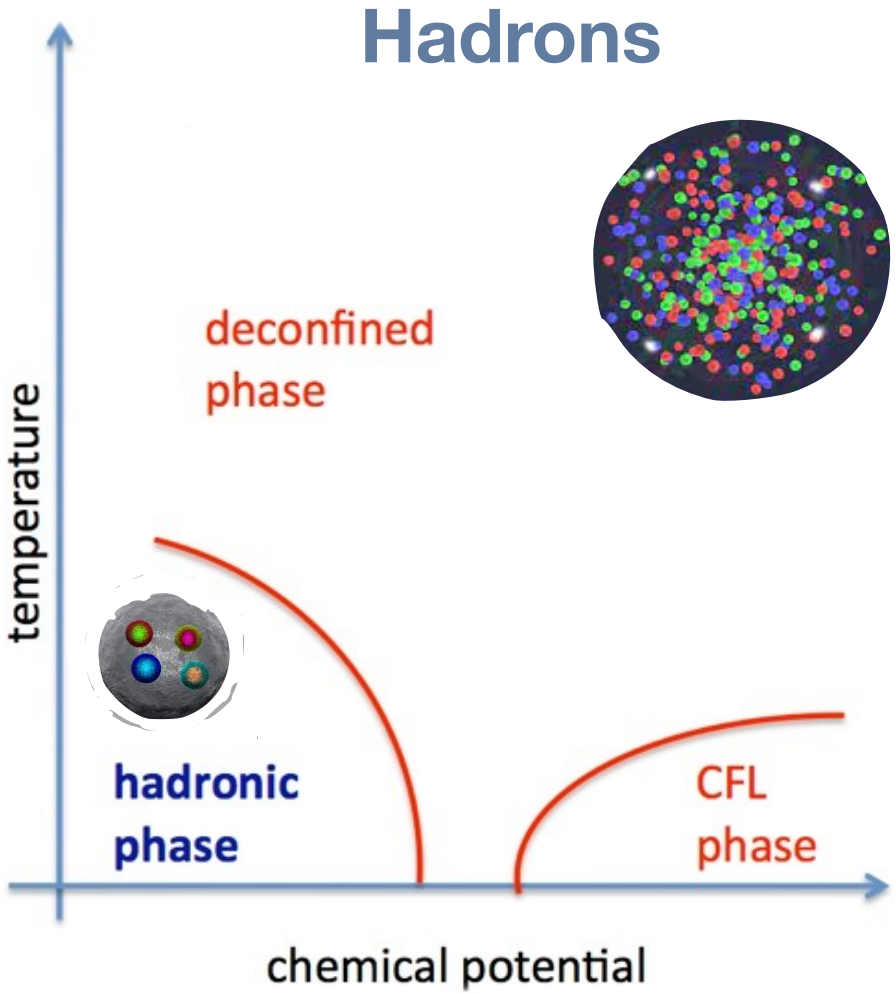


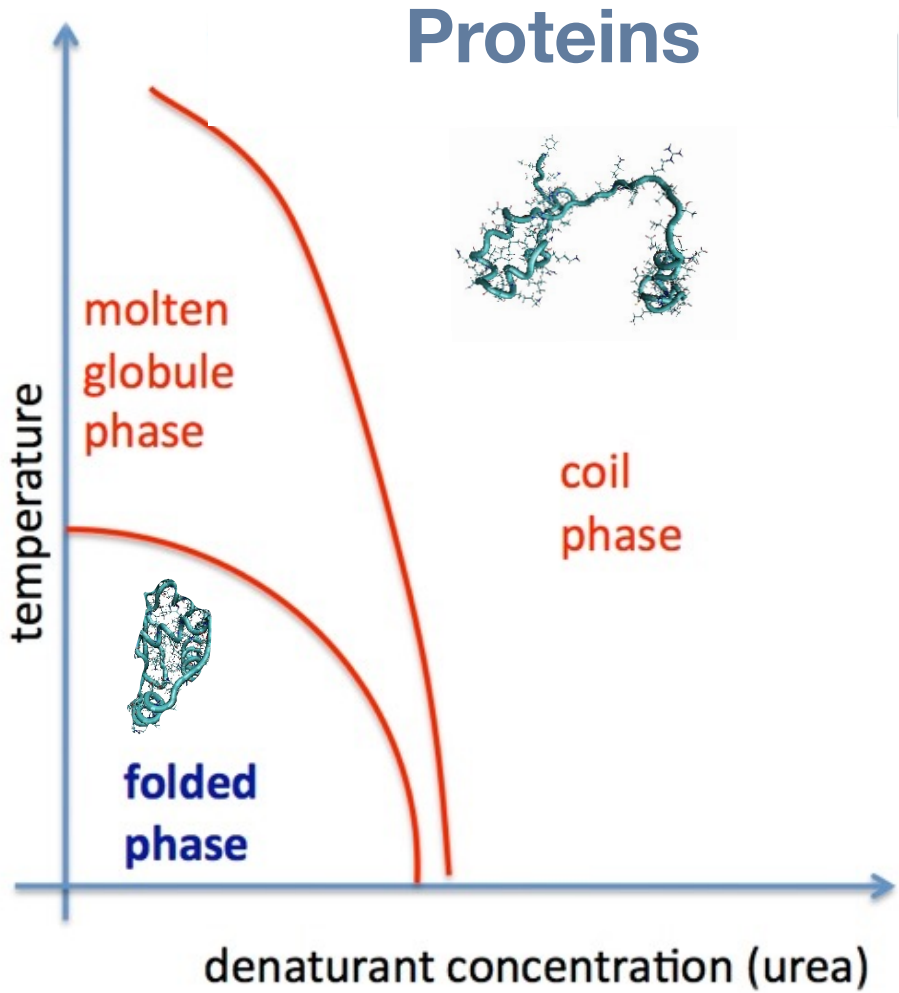




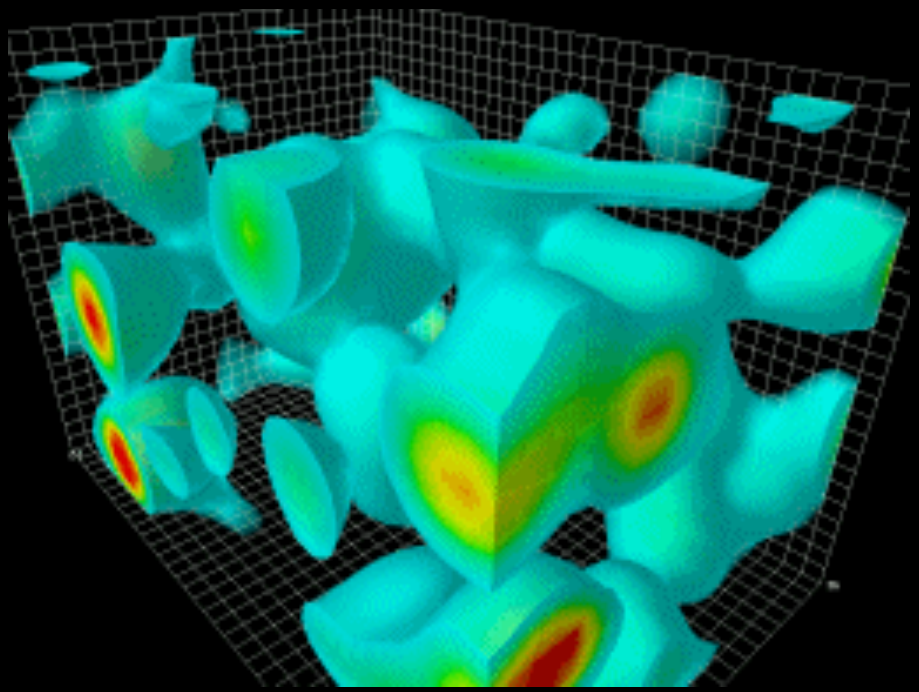
Source:
A. Shut and J. Onuchic, Curr. Open. Pharm. 2010
Matevosyan, Hray, , Ph.D. Thesis

PHASE DIAGRAM

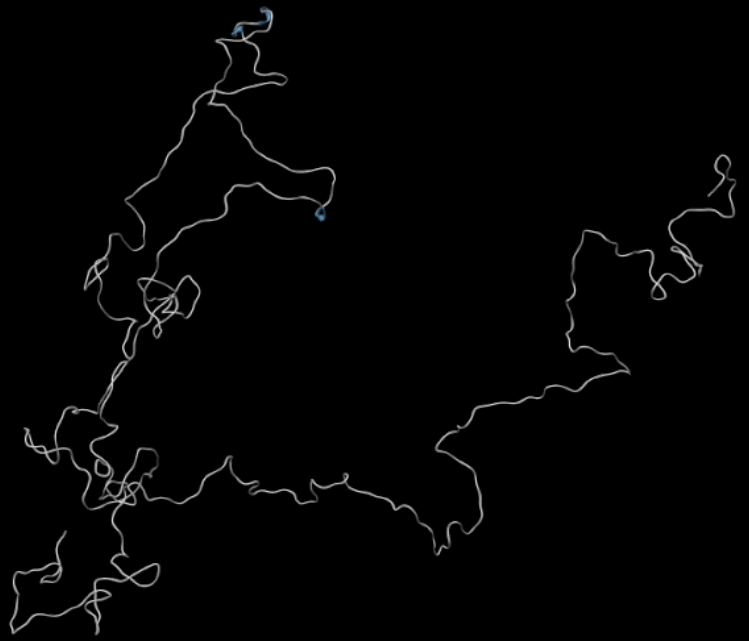




Proteins and hadrons are non-perturbative complex many-body systems



Topological gauge field fluctuations
in the QCD vacuum

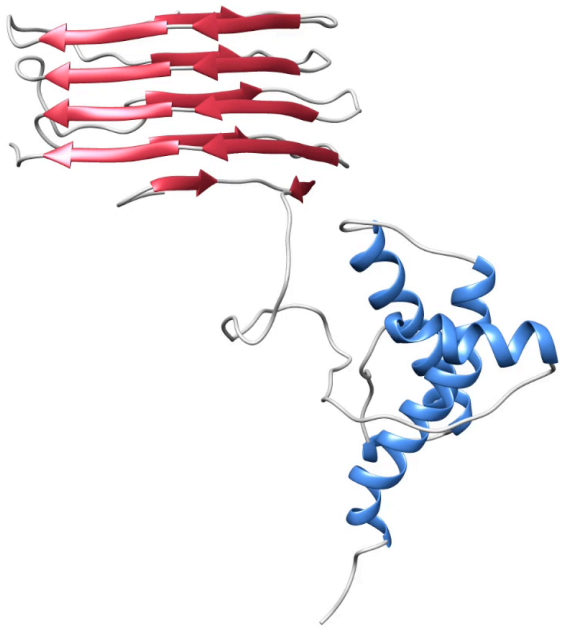


Protein folding

Can mathematical methods of high-energy physics be harnessed to study protein dynamics?

Source: D. Leinweber,, “Visualization of QCD”

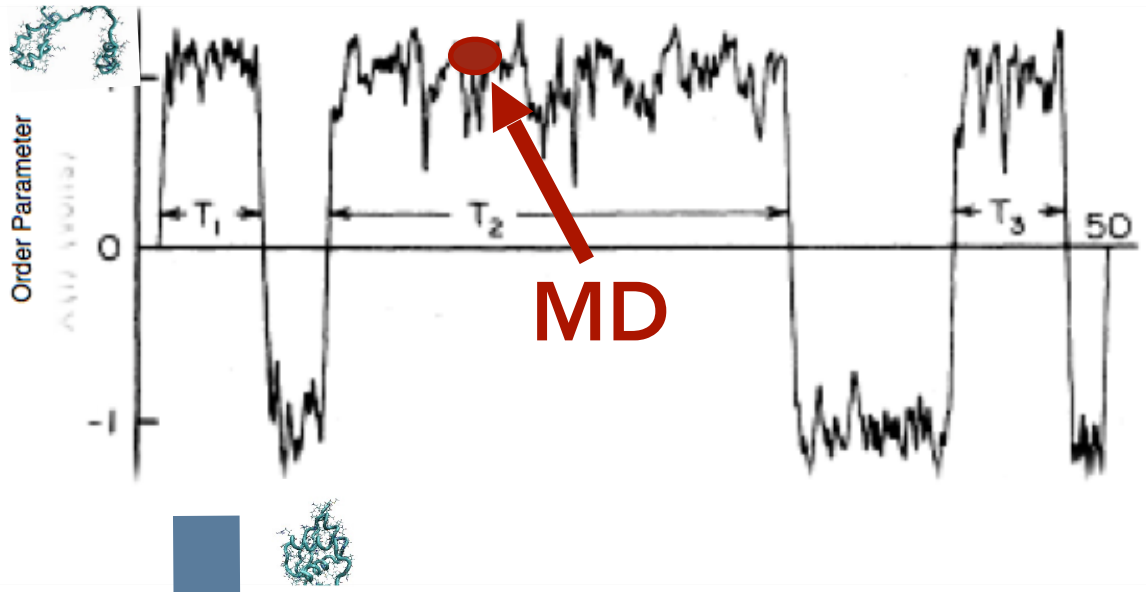
REDUCTIONIST'S APPROACH TO MOLECULAR BIOLOGY

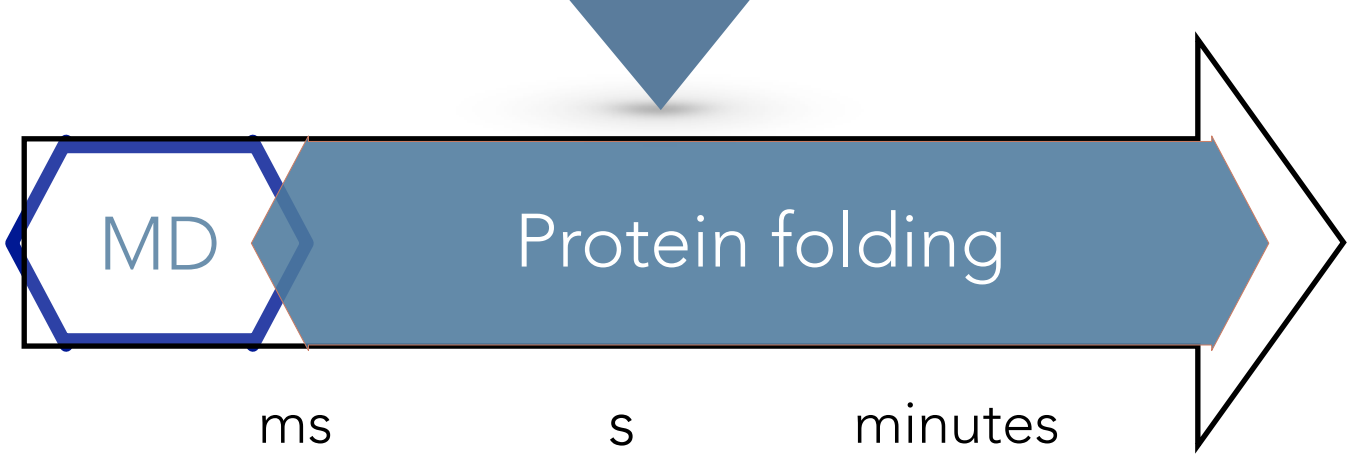


Challenge:

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

RARE EVENT PROBLEMS

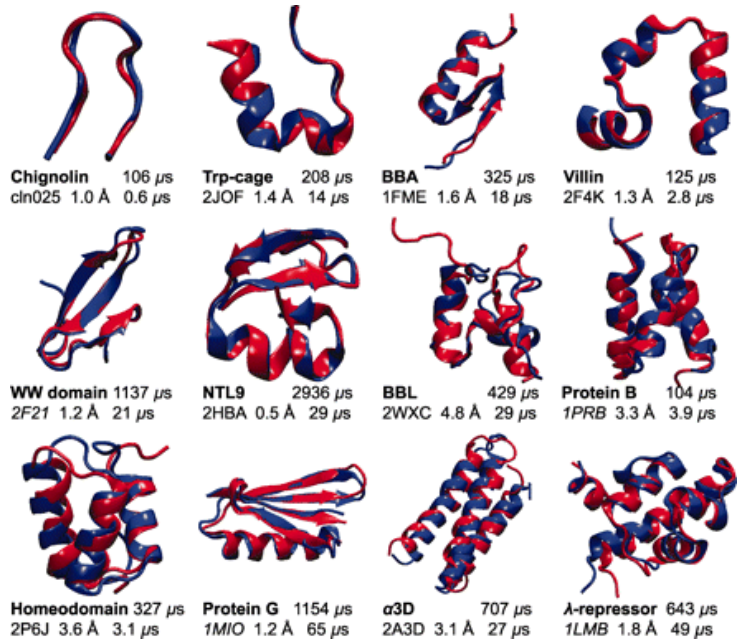




MD YIELDS CORRECT PROTEIN NATIVE STATES

Anton supercomputer
(DES Research)

MD



Science
AAAS

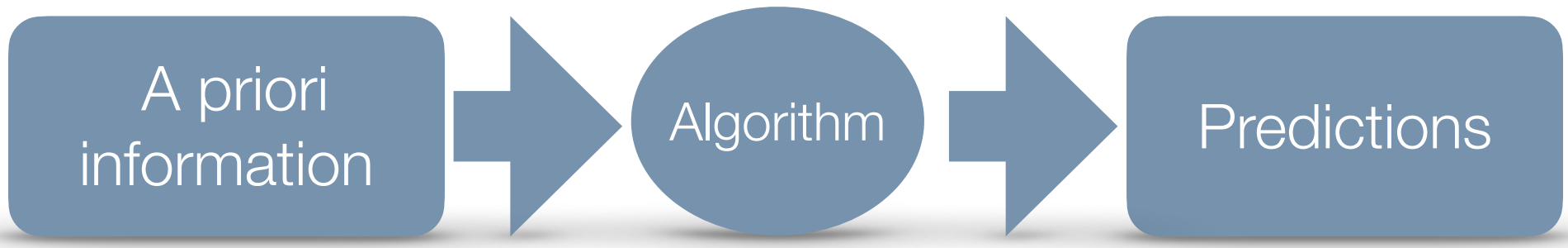
Atomic-Level Characterization of the Structural Dynamics of Proteins
David E. Shaw, *et al.*
Science **330**, 341 (2010);
DOI: 10.1126/science.1187409

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

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



VARIATIONAL APPROXIMATIONS TO TRANSITION PATH SAMPLING

Mathematical tools borrowed from subnuclear physics

New approximations and algorithms

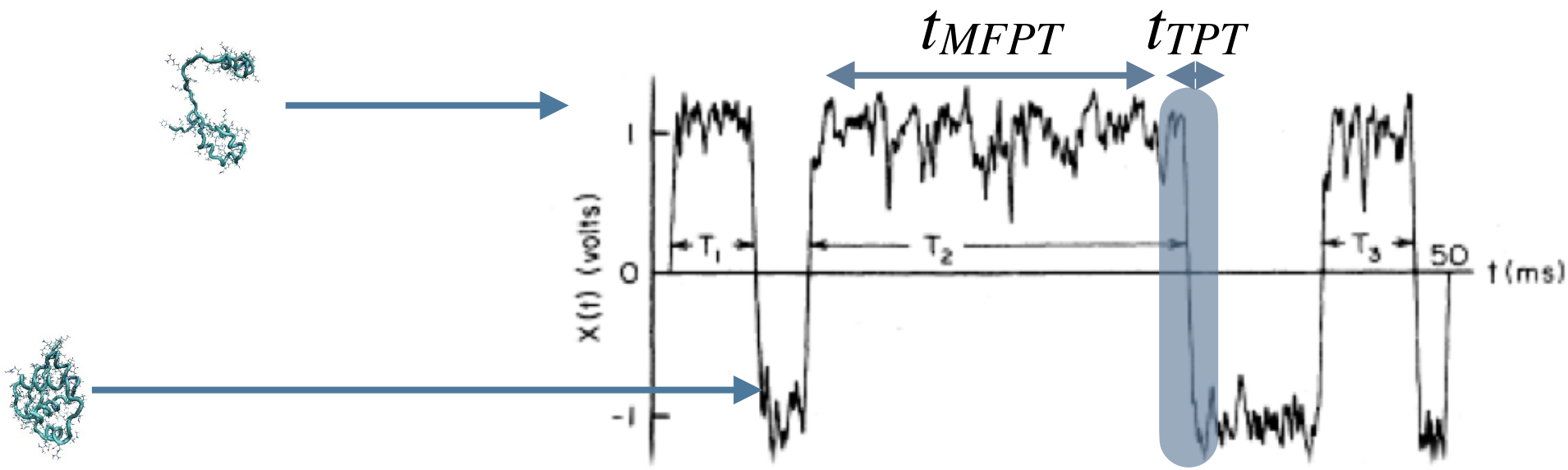
Thermal activation: $k_B T > 0$

$$P(x_f, t|x_i) = \frac{e^{-\frac{1}{2k_B T}U(x_f)}}{e^{-\frac{1}{2k_B T}U(x_i)}} \int_{x_i}^{x_f} \mathcal{D}Q \; e^{-\frac{1}{k_B T}\int_0^t d\tau \left(\frac{M\gamma}{4}\dot{Q}^2 + V_{eff}(Q)\right)}$$

Quantum Tunneling: $\hbar > 0$

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

ADVANTAGES OF PATH INTEGRALS



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

Still too expansive for realistic proteins**....we need approximations.**

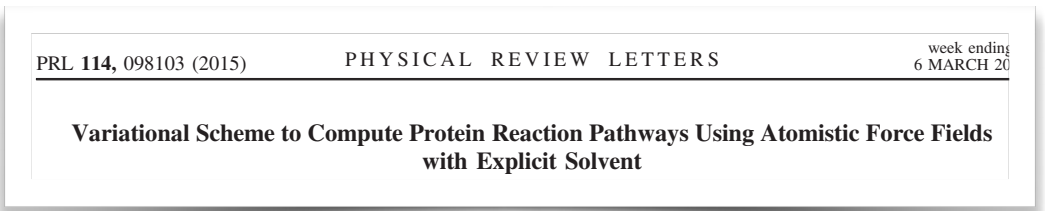
VARIATIONAL APPROXIMATIONS FOR TRANSITION PATH SAMPLING


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

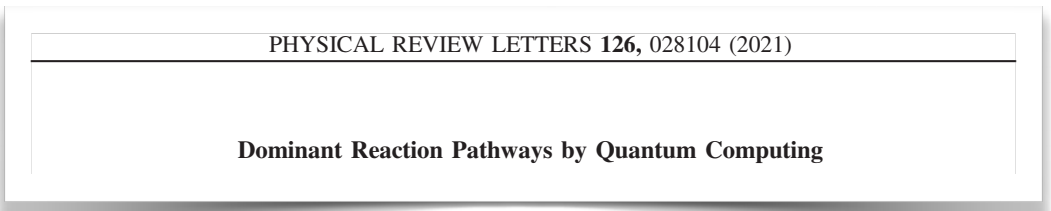
Dominant Pathways in Protein Folding


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

Quantitative Protein Dynamics from Dominant Folding Pathways


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


PHYSICAL REVIEW LETTERS **126,** 028104 (2021)

Dominant Reaction Pathways by Quantum Computing

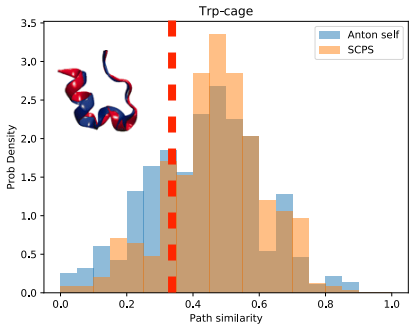
Variational Theorem

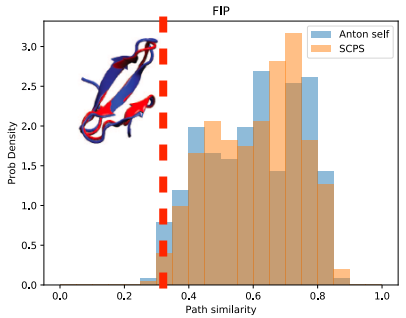
ANSATZ

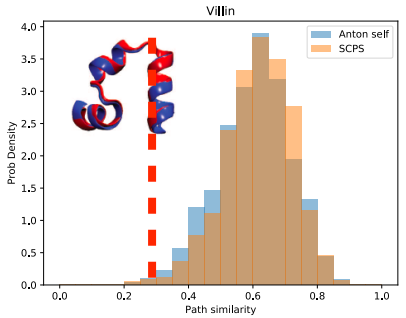
Prediction

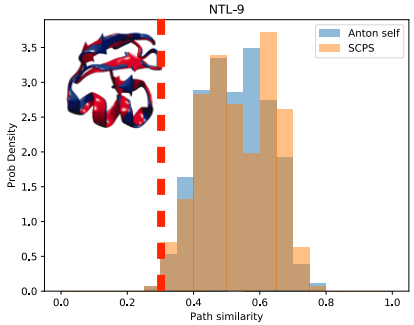
A priori information

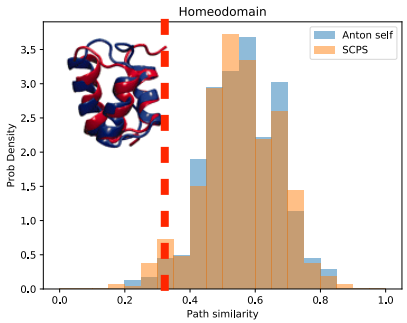
VALIDATING AGAINST BRUTE FORCE MD

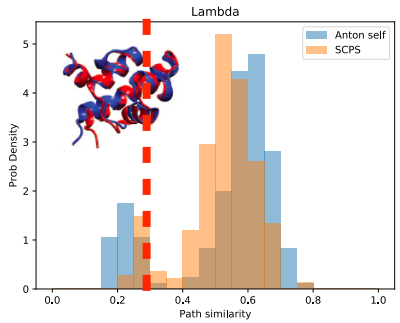


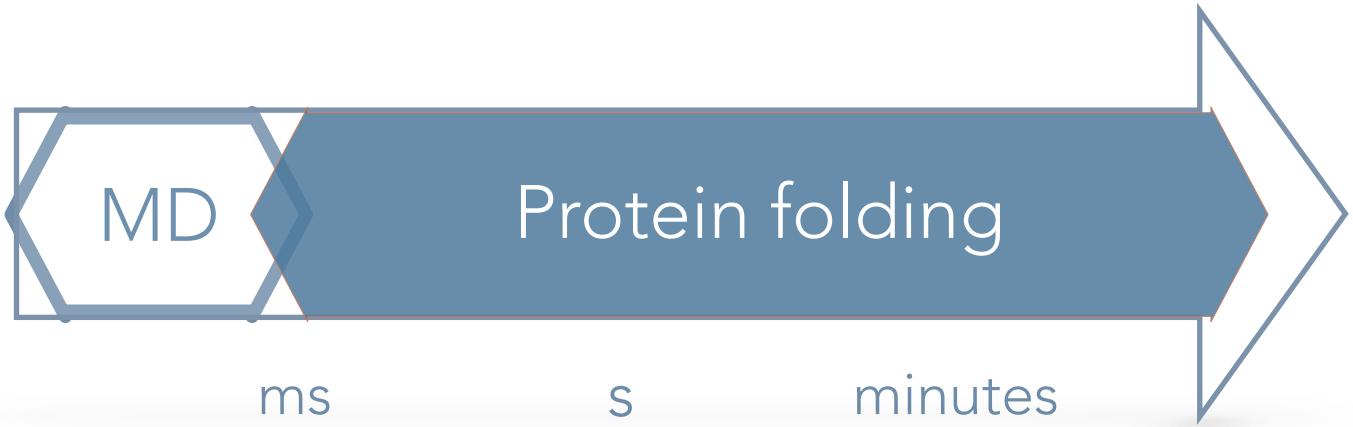




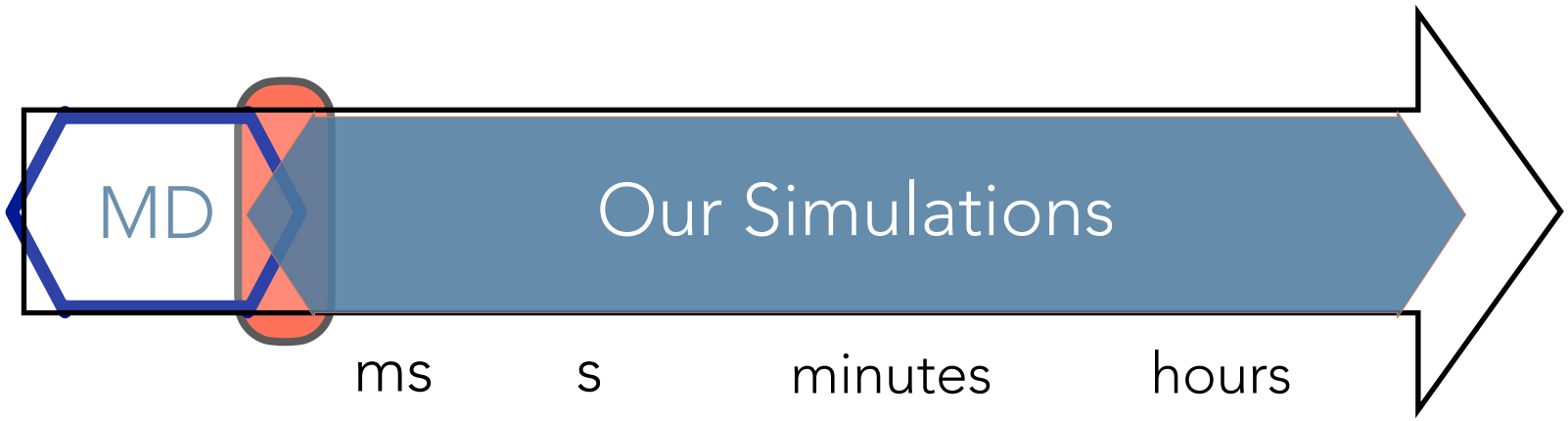


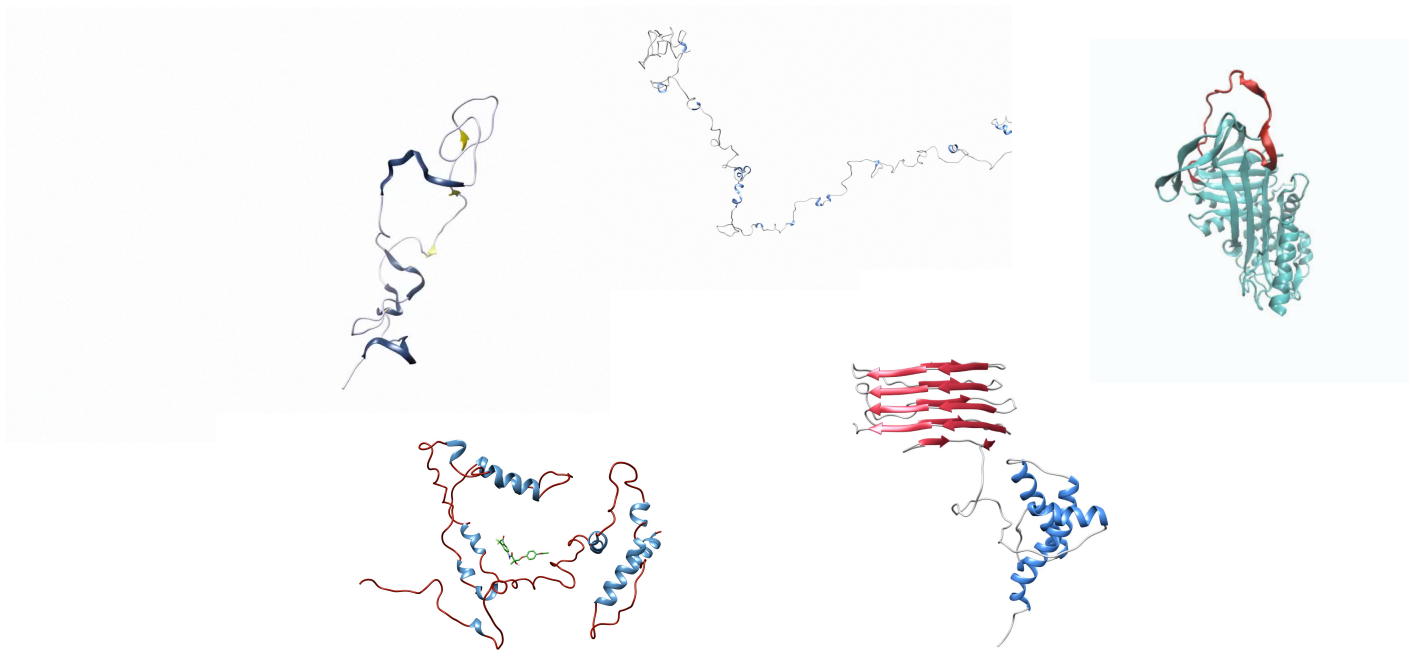




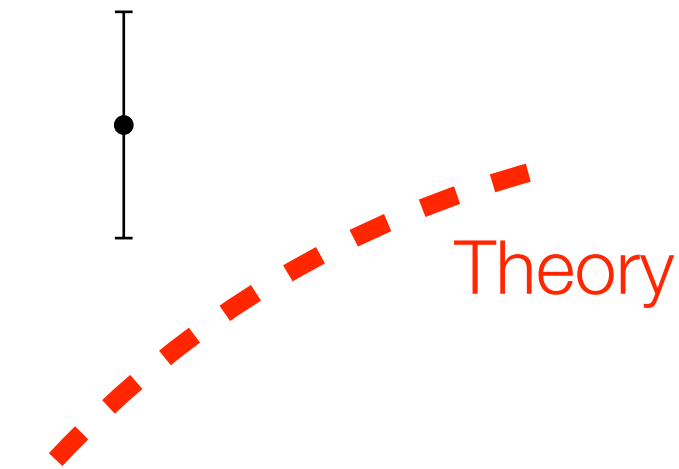


VENTURING INTO THE BIO-ZONE





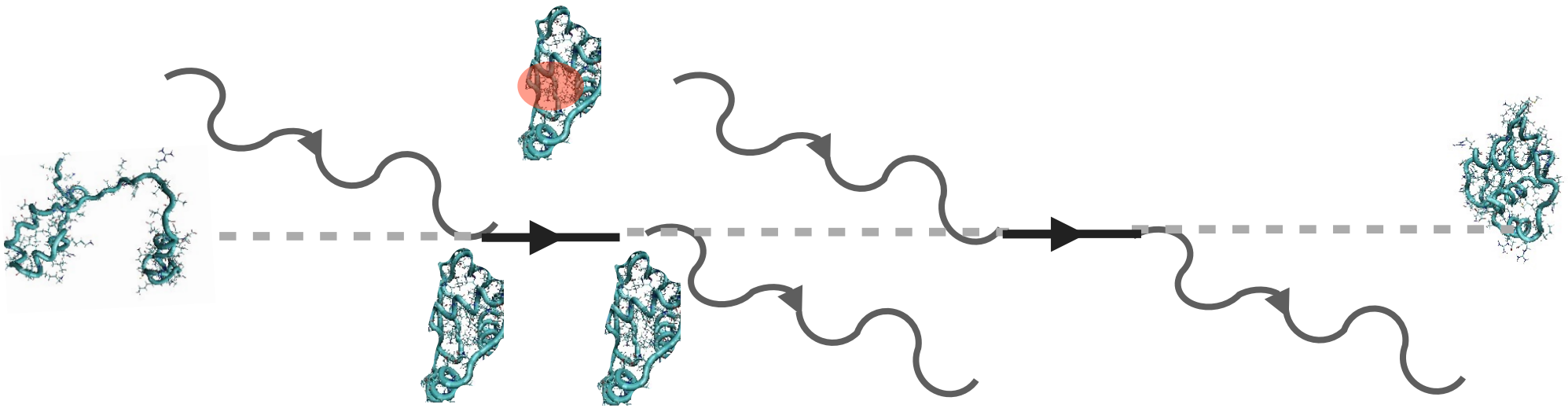
VALIDATION AGAINST EXPERIMENT



Challenge:

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

TIME-DEPENDENT SPECTROSCOPY



Ground state

Electronic excitation

Challenge:

non-equilibrium dynamics of **quantum electronic excitations** in conformationally evolving proteins

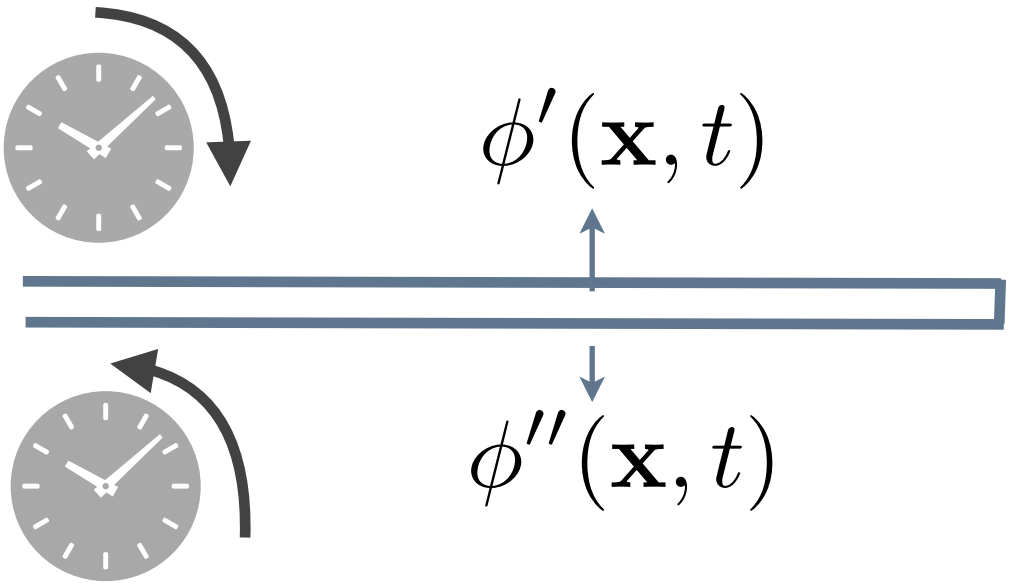
THE CHALLENGE OF NON-EQUILIBRIUM

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

multiple time directions…

HELP FROM THE "RELATIVISTIC" QUANTUM FIELD THEORY FORMALISM

The mathematical formalism of relativistic QFT formalism enables us to 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)

DENSITY MATRIX IN MQFT

$$\rho = \left(\begin{array}{c|ccc|ccc} \rho_{gg} & \rho_{ge_1} & \cdots & \rho_{ge_N} & \rho_{g\alpha_1} & \cdots & \rho_{g\alpha_{N_2}} \\ \hline \rho_{e_1 g} & \rho_{e_1 e_1} & \cdots & \rho_{e_1 e_N} & \rho_{e_1 \alpha_1} & \cdots & \rho_{e_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{e_N g} & \rho_{e_N e_1} & \cdots & \rho_{e_N e_N} & \rho_{e_N \alpha_1} & \cdots & \rho_{e_N \alpha_{N_2}} \\ \hline \rho_{\alpha_1 g} & \rho_{\alpha_1 e_1} & \cdots & \rho_{\alpha_1 e_N} & \rho_{\alpha_1 \alpha_1} & \cdots & \rho_{\alpha_1 \alpha_{N_2}} \\ \vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ \rho_{\alpha_{N_2} g} & \rho_{\alpha_{N_2} e_1} & \cdots & \rho_{\alpha_{N_2} e_N} & \rho_{\alpha_{N_2} \alpha_1} & \cdots & \rho_{\alpha_{N_2} \alpha_{N_2}} \end{array}\right)$$

Structural dynamics $\rho_{gg} \propto \int DR e^{-S_{OM}[R]}$

Linear Spectroscopy: $\rho_{e_k g}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\ e^{iS_{tot}}\ \psi(e_l, t)\ \bar{\psi}(e_n, 0)$

Quantum Mobility: $\rho_{e_k e_l}(t) \propto \int \mathcal{D}\delta R \int \mathcal{D}\psi \mathcal{D}\bar{\psi}\ e^{iS_{tot}}\ \bar{\psi}(e_l, t)\gamma_- \gamma_5 \psi(e_k, t)\ \bar{\psi}(e_n, 0)\gamma_+ \gamma_5 \psi(e_m, 0)$

Non-linear spectroscopy: ....

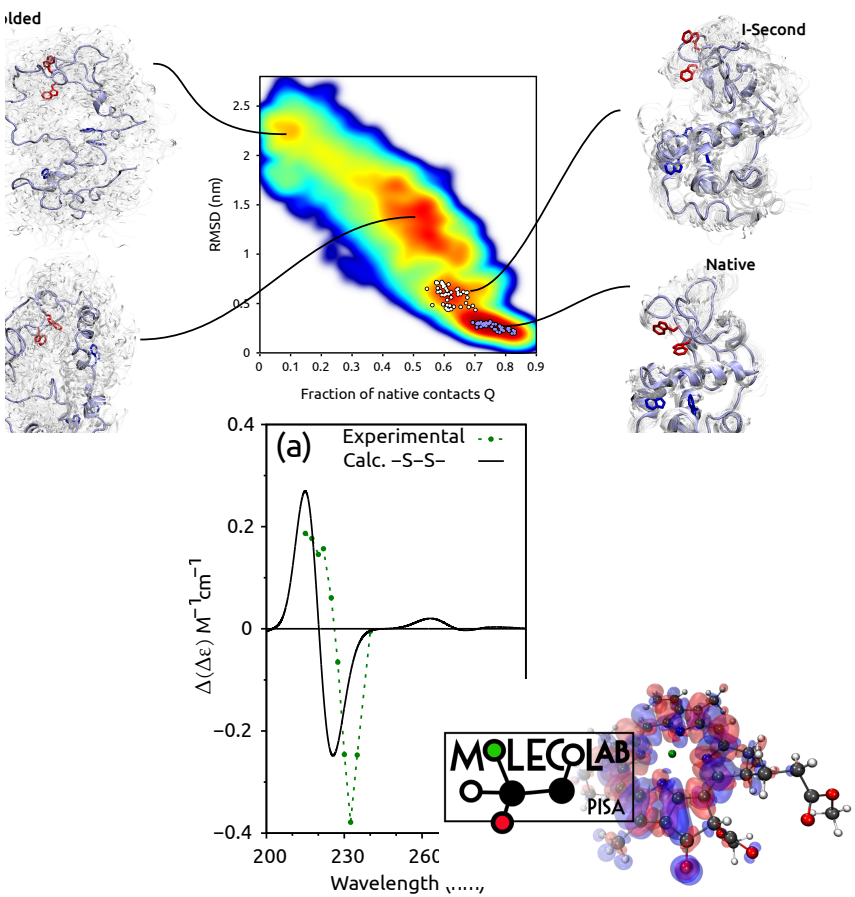
DIRECT COMPARISON AGAINST EXPERIMENT

with B. Mennucci's Lab (Pisa)

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[*,§]

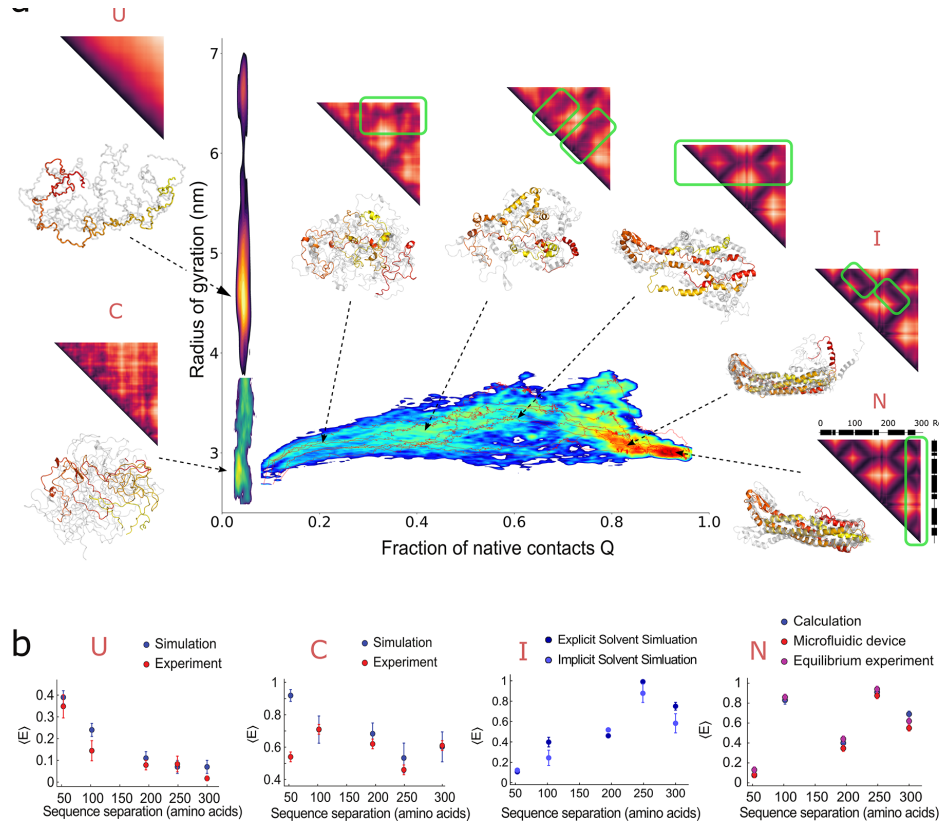


with B. Schuler's Lab (U. Zurich)

J|A|C|S Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/jacsau
Article

Slow Escape from a Helical Misfolded State of the Pore-Forming Toxin Cytolysin A

Fabian Dingfelder, Iuri Macocco, Stephan Benke, Daniel Nettels, Pietro Faccioli,* and Benjamin Schuler*



THREE PIVOTAL QUESTIONS FOR THIS TALK

Can mathematical methods of high-energy physics be harnessed to address biologically relevant questions?

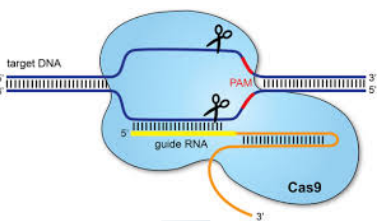
Can we generate new insight to envision new therapeutic strategies?

What do emerging technologies have to offer?

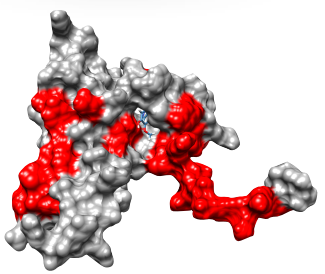
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING

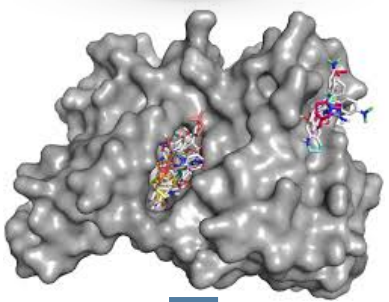
patent file # 102018000007535 (with E. Biasini)

DNA → mRNA → Ribosome → Protein folding → Protein function



RNA silencing





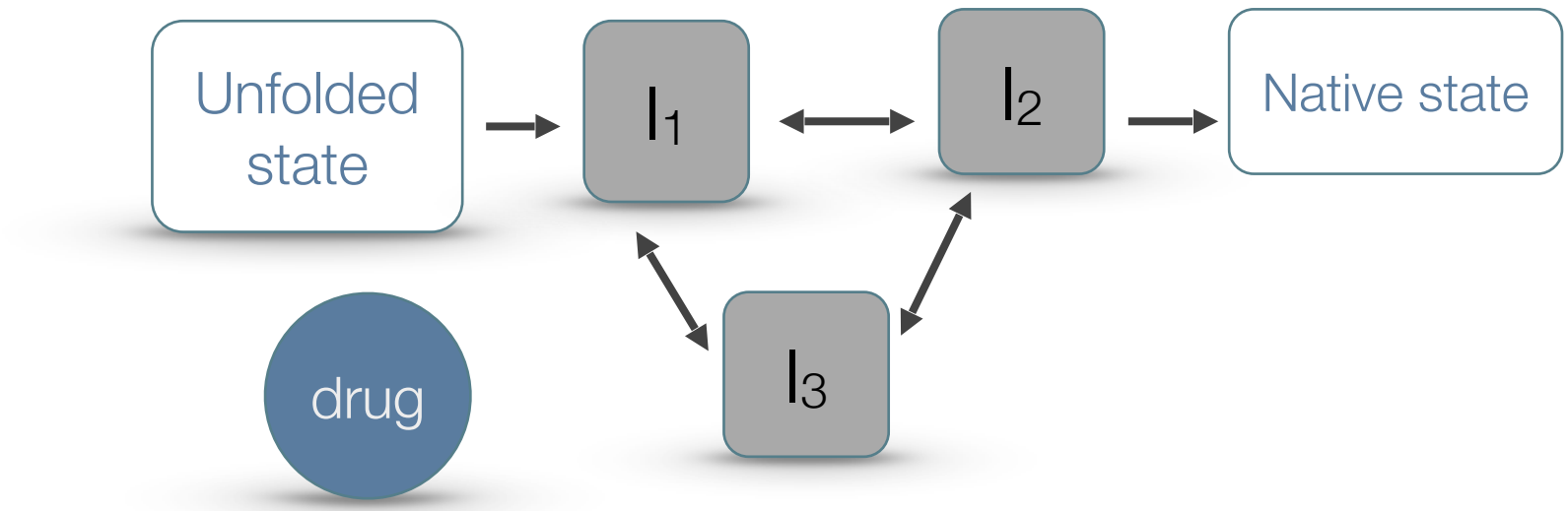
Eliminating protein from genome

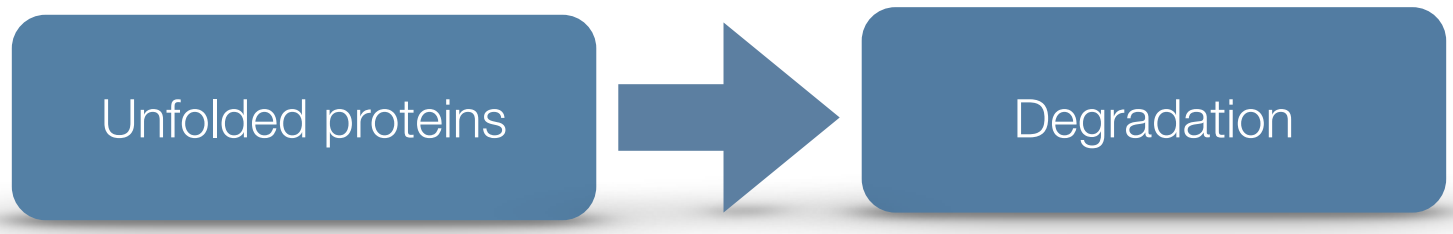
Suppressing transcription

Suppressing folding

Imparing function

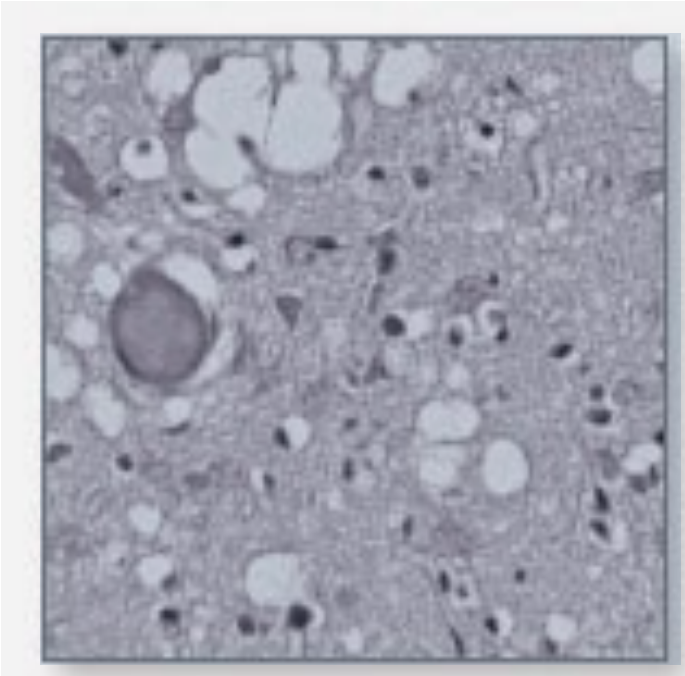
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING



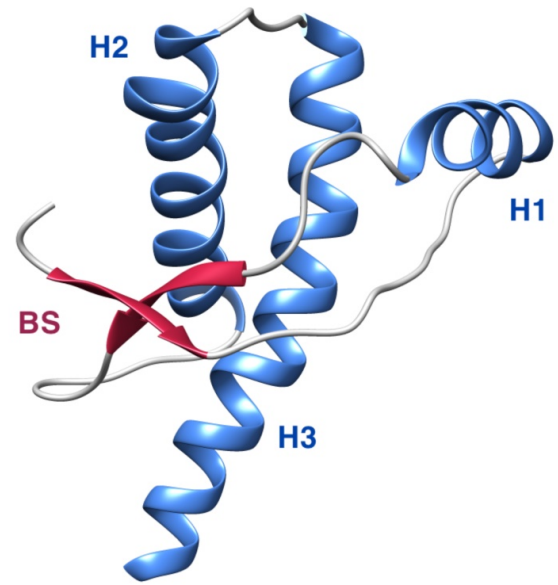


DRUGGING THE UNDRUGGABLE

PRION DISEASES



PRION PROTEIN



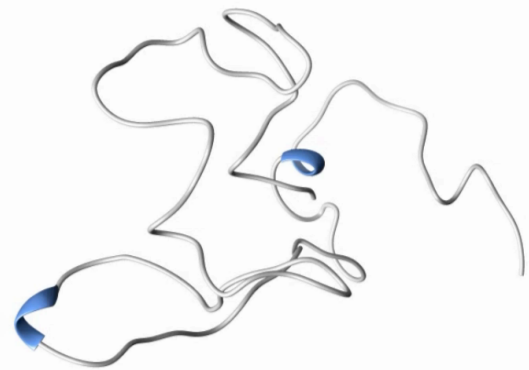
nature › communications biology › articles › article

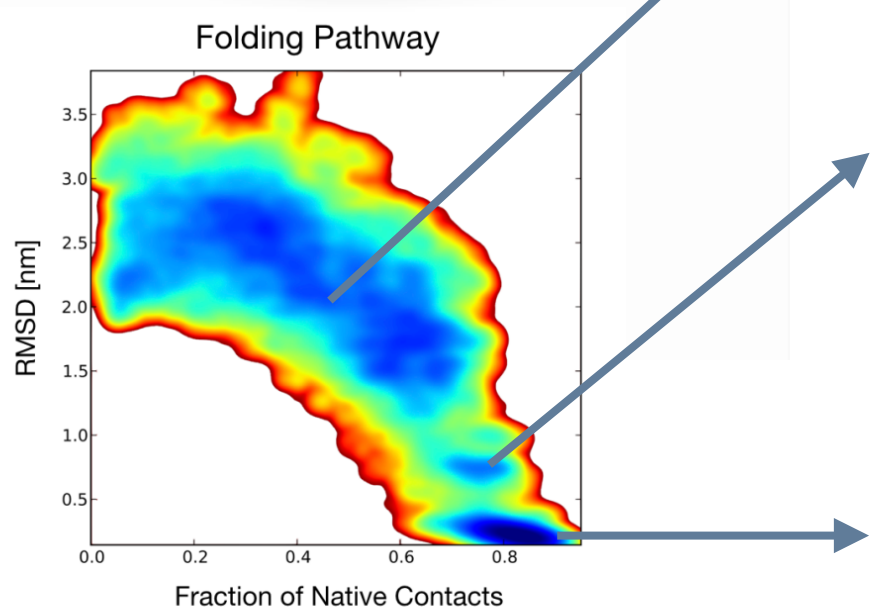
Article | Open Access | Published: 12 January 2021

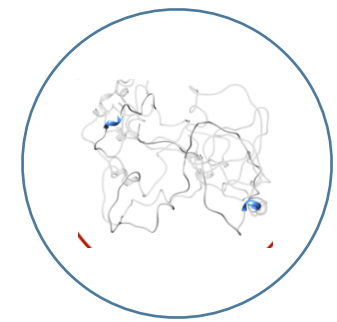
Pharmacological inactivation of the prion protein by targeting a folding intermediate

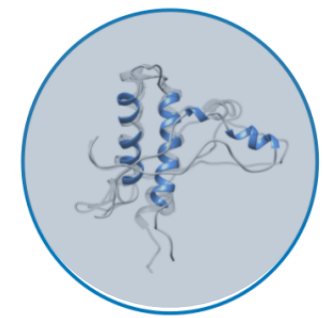
PPI-FIT PROOF-OF-CONCEPT

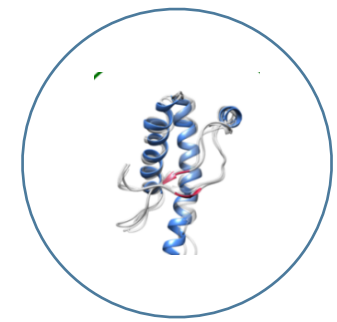
Folding pathway characterization







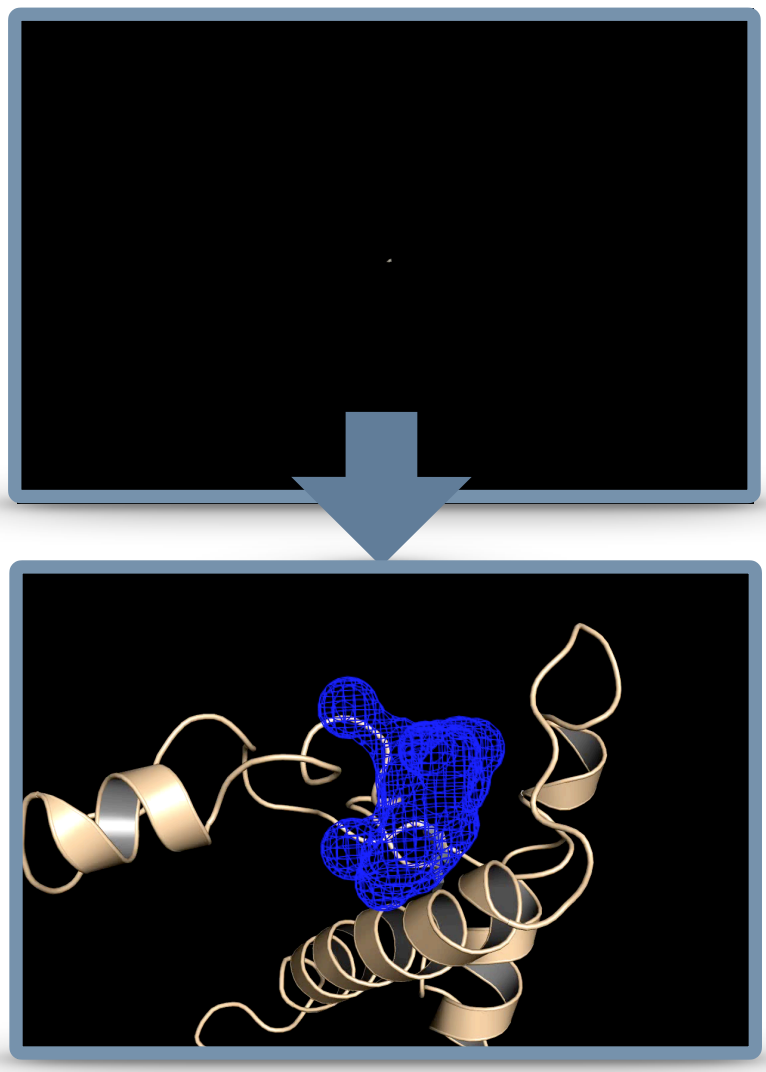




PPI-FIT PROOF-OF-CONCEPT

Folding pathway characterization

Virtual screening on folding Intermediate

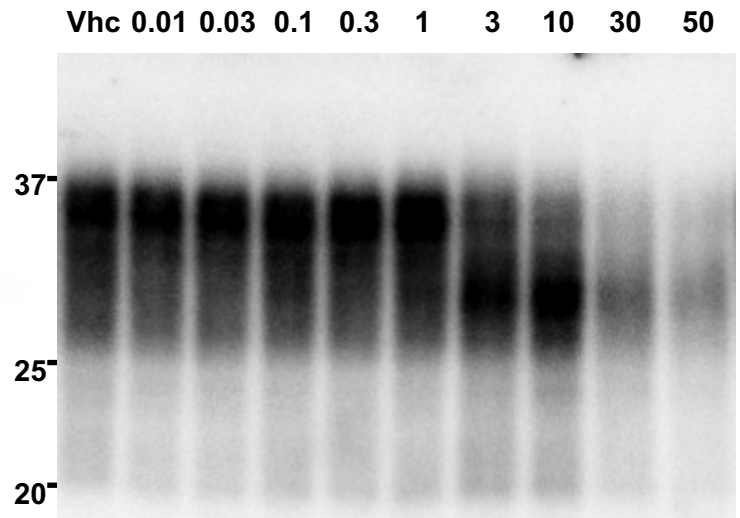


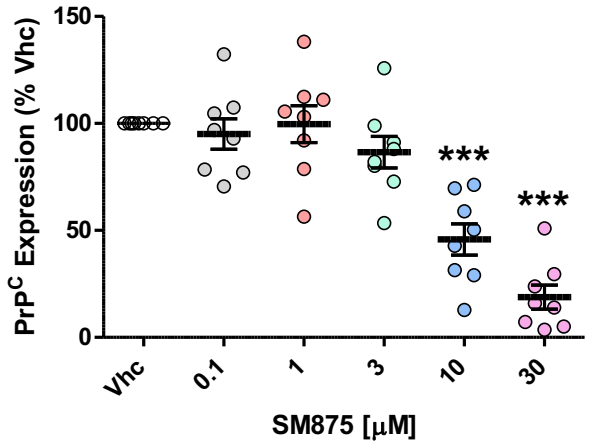
PPI-FIT PROOF-OF-CONCEPT

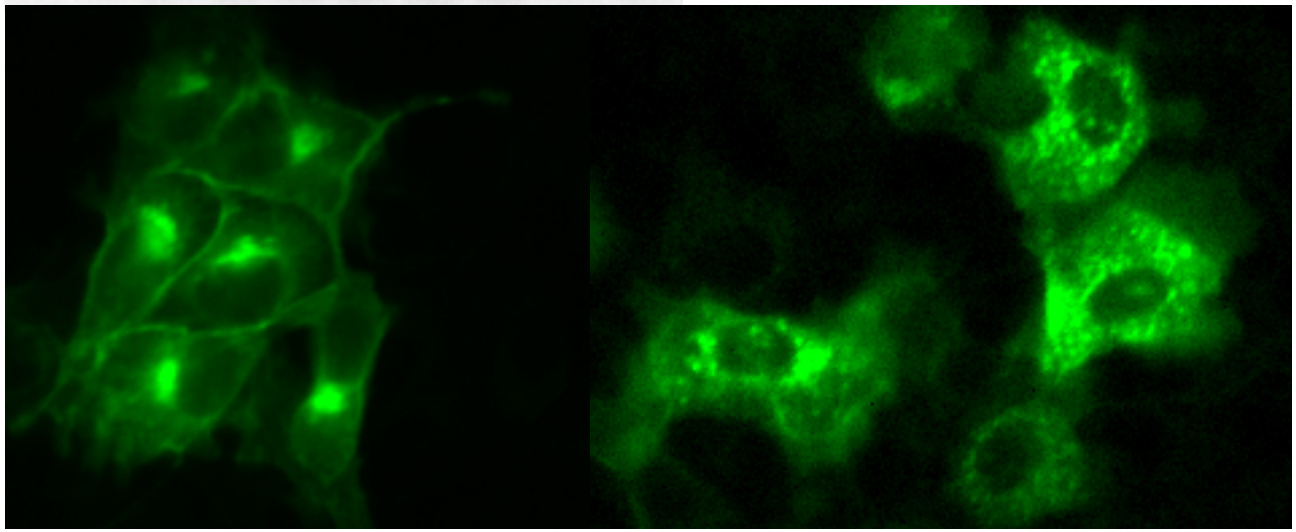
Folding pathway characterization

Virtual screening on folding Intermediate

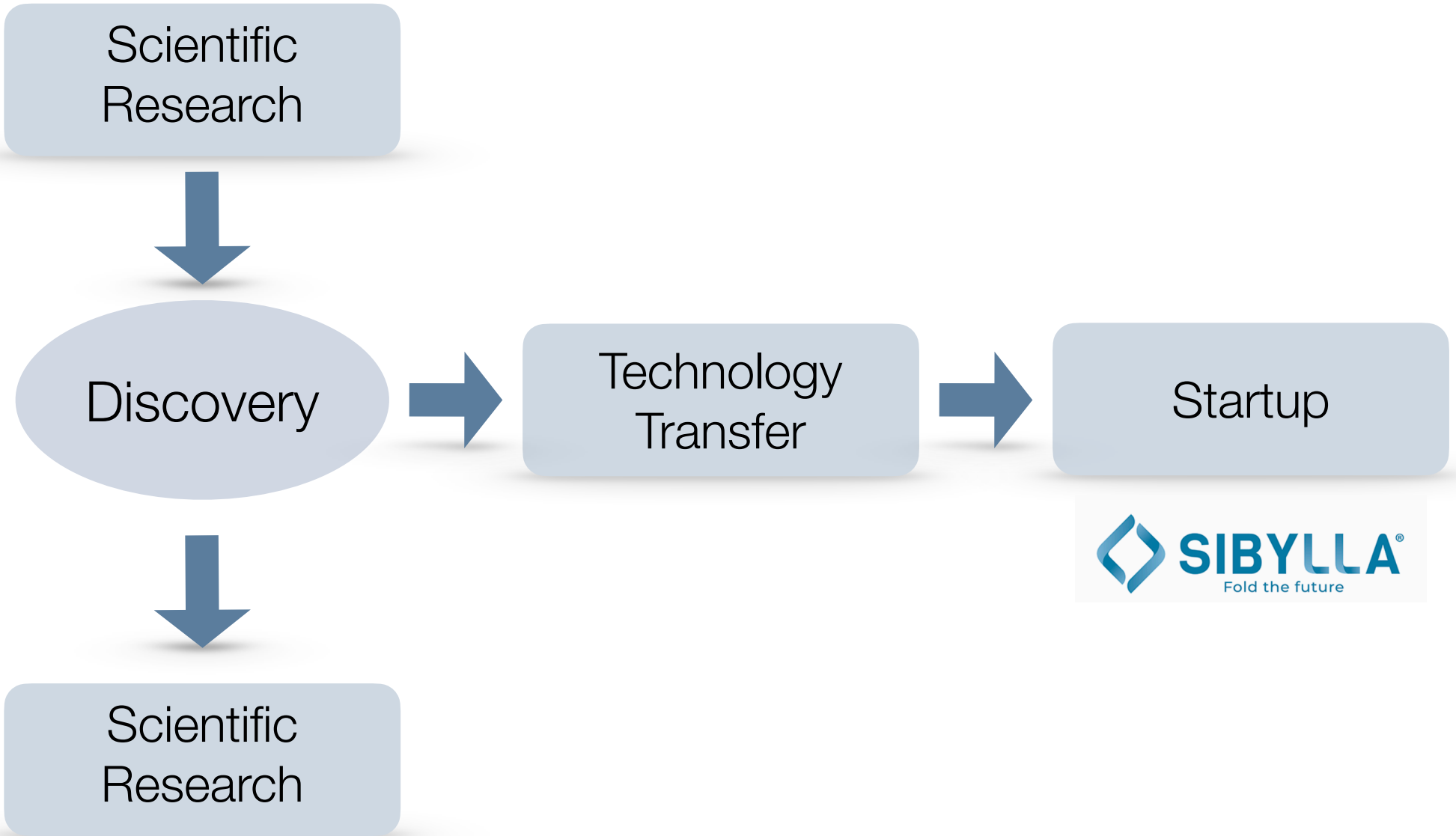
Biochemical Validation





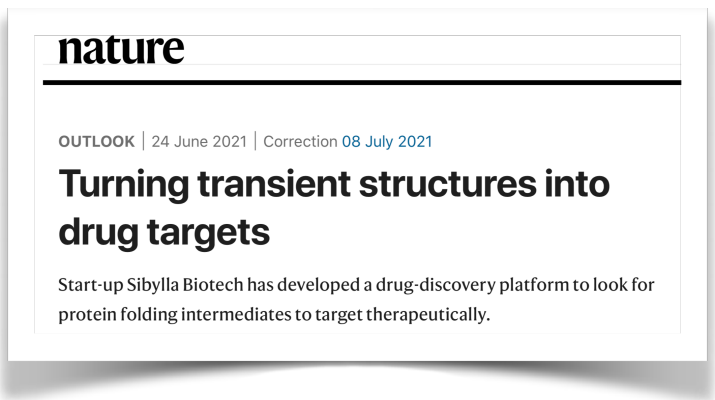


TECHNOLOGY TRANSFER INITIATIVE



SIBYLLA®
Fold the future

- **FUNDING** (by Venture Capital)
  - Seed: **2.4 MEUR (2020)**
  - Series-A: **23 MEUR (2022)**
- Selected in the **8 world finalist** of the **2021 Nature Spinoff Prize**



nature

OUTLOOK | 24 June 2021 | Correction 08 July 2021

Turning transient structures into drug targets

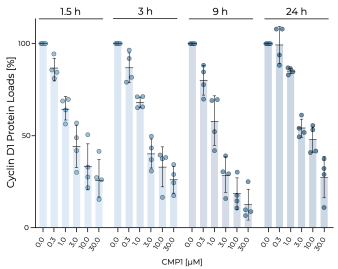
Start-up Sibylla Biotech has developed a drug-discovery platform to look for protein folding intermediates to target therapeutically.

- Selected in the **world finalist** of the **"One Thousands Startups Prize"** (2021)

SIBYLLA®
Fold the future

- Partnerships and services with Big-pharma (e.g. **TAKEDA** Pharmaceutics -2021-)

- Developed **internal pipelines** and found **additional evidence** for PPI-FIT on several targets in **different therapeutic areas**

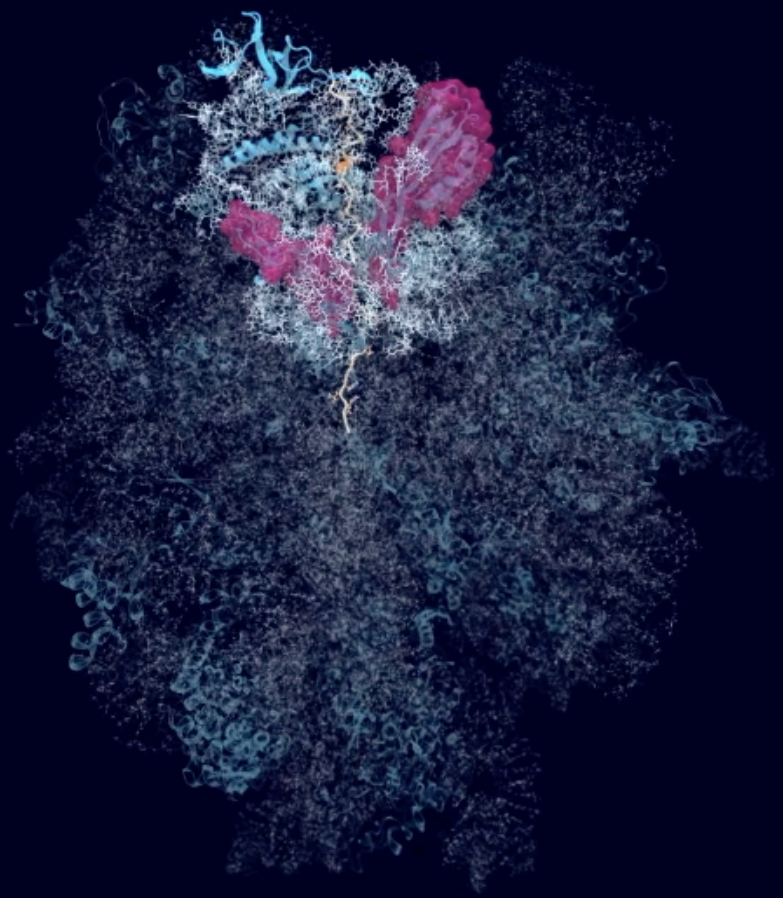


- Successful **Structure Activity Relationship**

- **Further developing the Science** underlying its technology

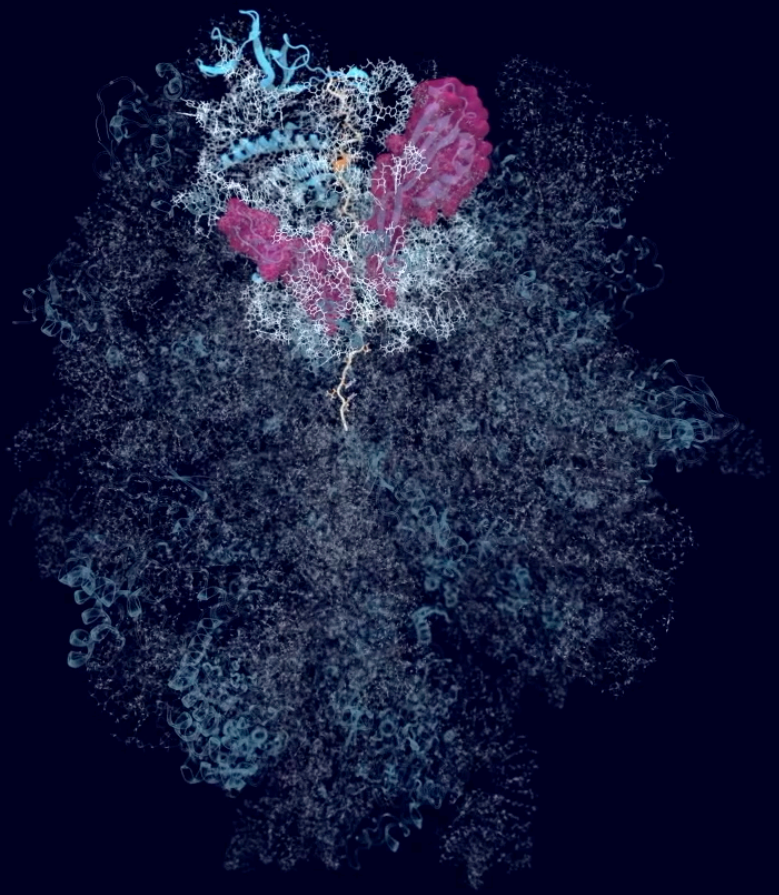
…folding in cell occurs co-translationally

typical “Anton” miniprotein



…folding in cell occurs co-translationally

SIBYLLA
Fold the future



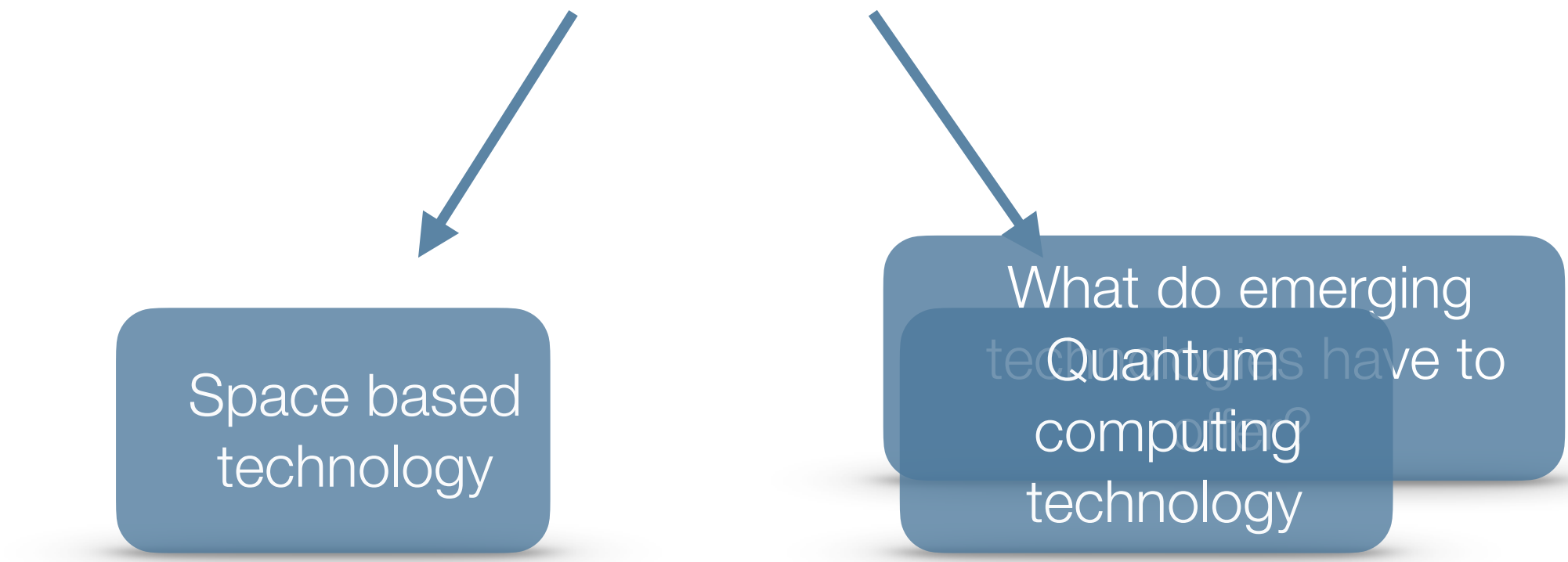
THREE PIVOTAL QUESTIONS FOR THIS TALK

Can mathematical methods of high-energy physics be harnessed to address biologically relevant questions?

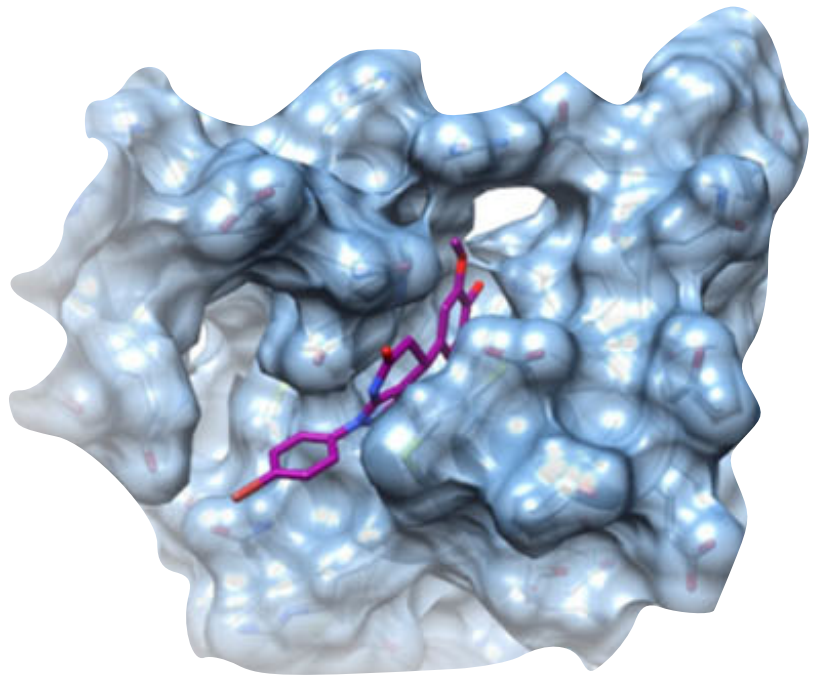
Can we generate new insight to envision new therapeutic strategies?

What do emerging technologies have to offer?

THREE PIVOTAL QUESTIONS FOR THIS TALK

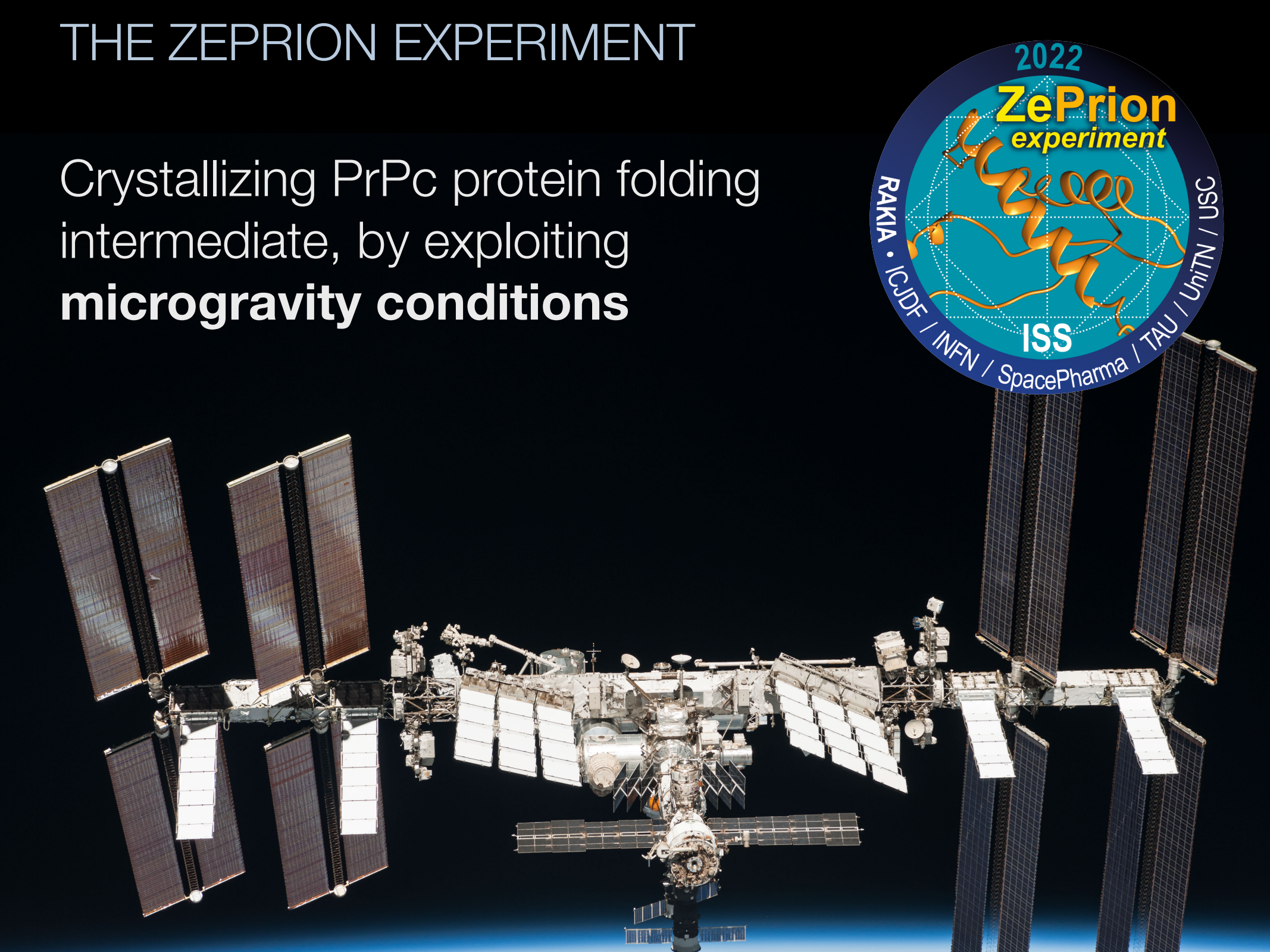


….STILL MISSING A CRYSTALLOGRAPHIC PROOF….

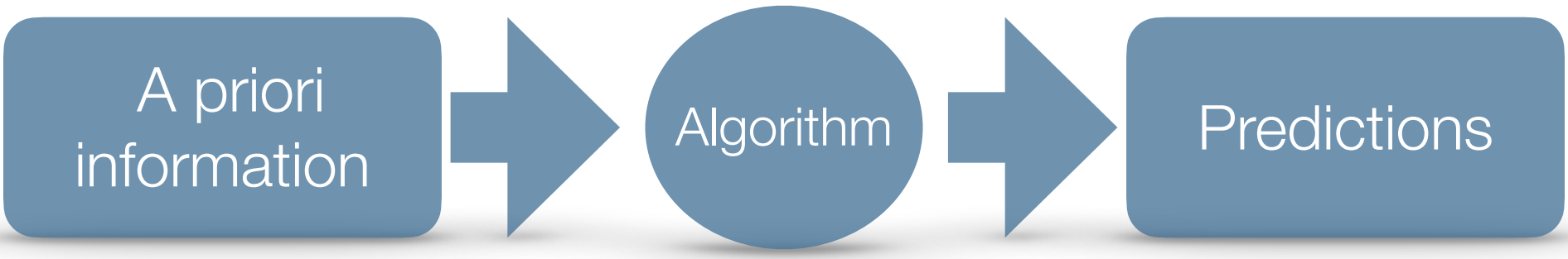


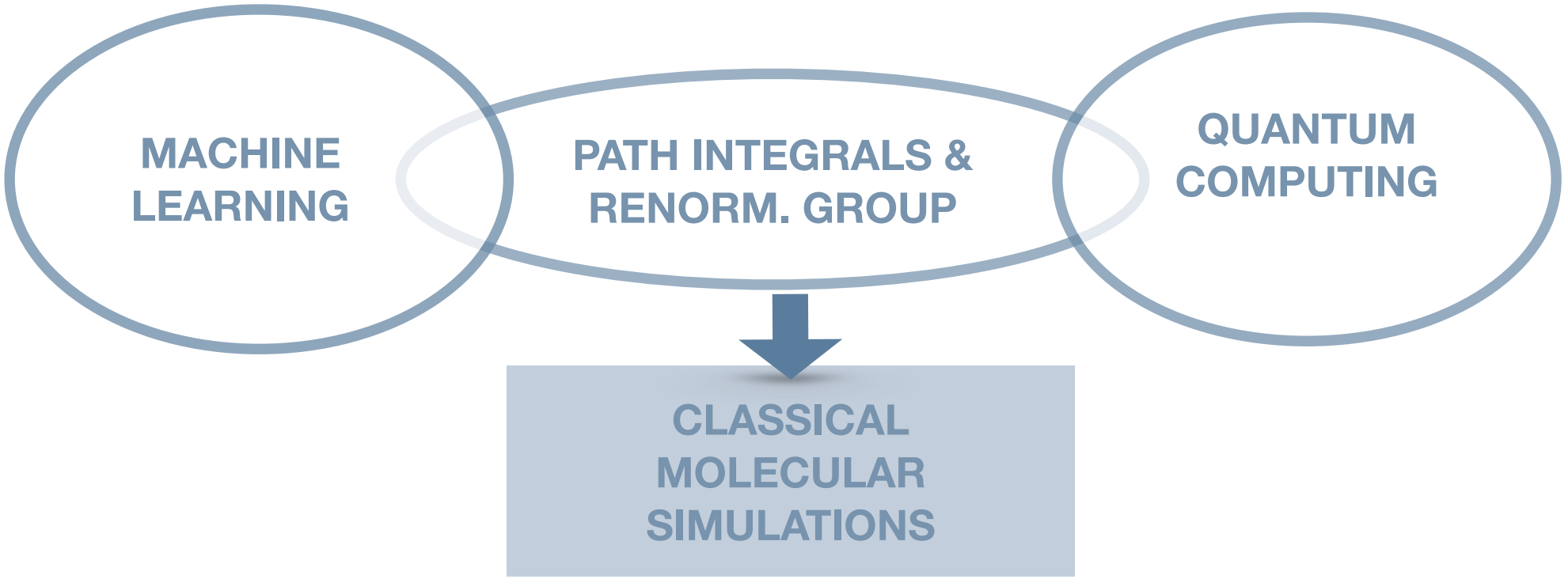
THE ZEPRION EXPERIMENT

Crystallizing PrPc protein folding intermediate, by exploiting **microgravity conditions**



TOWARD THE NEXT GENERATION OF MOLECULAR SIMULATIONS





Sampling Rare Conformational Transitions with a Quantum Computer

Danial Ghamari,[1,2] Philipp Hauke,[3] Roberto Covino,[4,*] and Pietro Faccioli[1,2,†]

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

Dominant Pathways in Protein Folding

99, 118102 (2007) PHYSICAL REVIEW LETTERS 14 S

Quantitative Protein Dynamics from Dominant Folding Pathways

PHYSICAL REVIEW LETTERS **127,** 080501 (2021)

Polymer Physics by Quantum Computing

Cristian Micheletti,[1,*] Philipp Hauke,[2] and Pietro Faccioli[3,†]

PHYSICAL REVIEW LETTERS **126,** 028104 (2021)

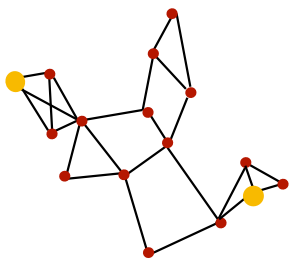
Dominant Reaction Pathways by Quantum Computing

Philipp Hauke,[1] Giovanni Mattiotti,[2] and Pietro Faccioli[2,3]

Task carried out on a quantum computer

Task carried out on a classical computer

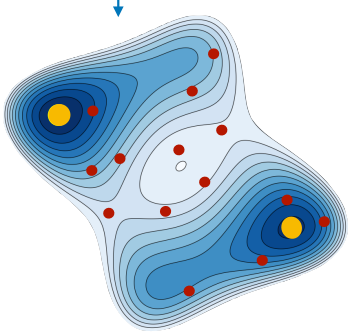
CLASSICAL MOLECULAR SIMULATIONS



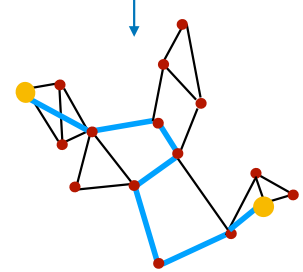
$t_{\text{sweep}} \rightarrow t'_{\text{sweep}}$

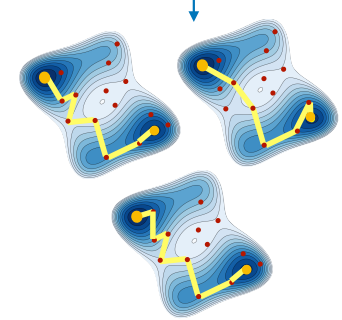
$$\min\left[1, \frac{P(t'_{\text{sweep}} \rightarrow t_{\text{sweep}})}{P(t_{\text{sweep}} \rightarrow t'_{\text{sweep}})} \times \frac{P(\mathbf{I}|t_{\text{sweep}})}{P(\mathbf{I}'|t'_{\text{sweep}})} \times \frac{e^{-S(\mathbf{I}')}}{e^{-S(\mathbf{I})}}\right]$$

Intrinsic Manifold exploration → Graph construction → Transition probability calculation → Update of quantum annealing time → Trial transition path generation → Accept or reject → **Transition Path Ensemble**



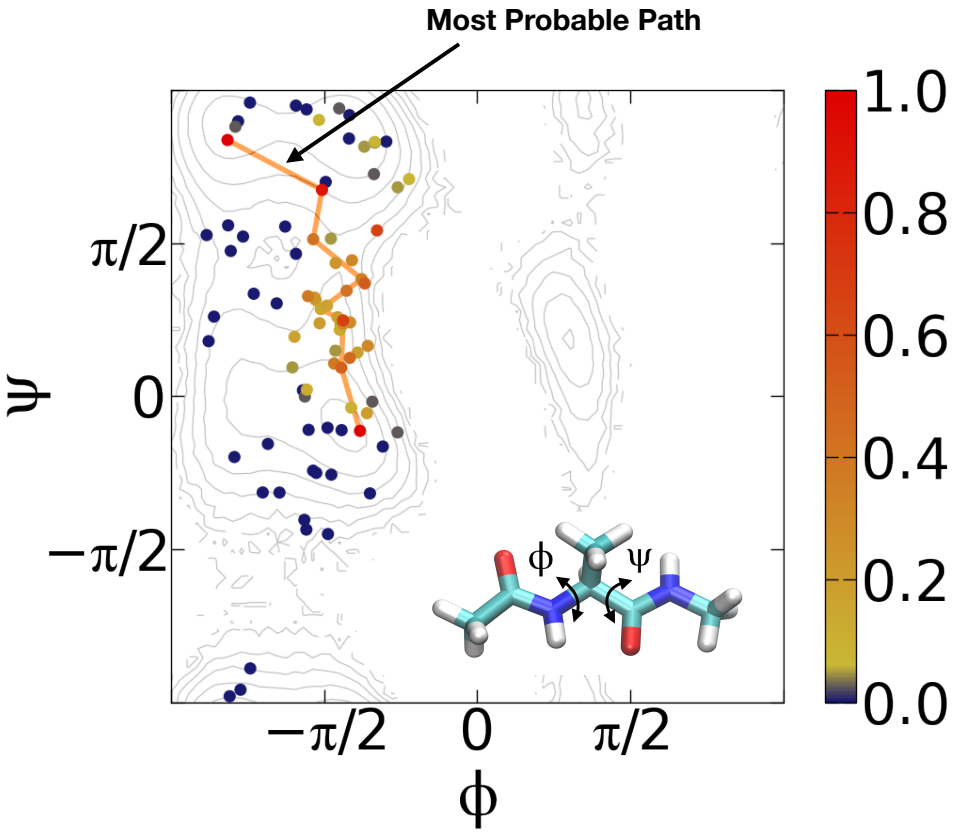
$$P(\mathbf{I}|t_{\text{sweep}}) \simeq \frac{1}{\sqrt{2\pi}\Delta} e^{-\frac{(S(\mathbf{I})-\overline{S})^2}{2\Delta^2}}$$



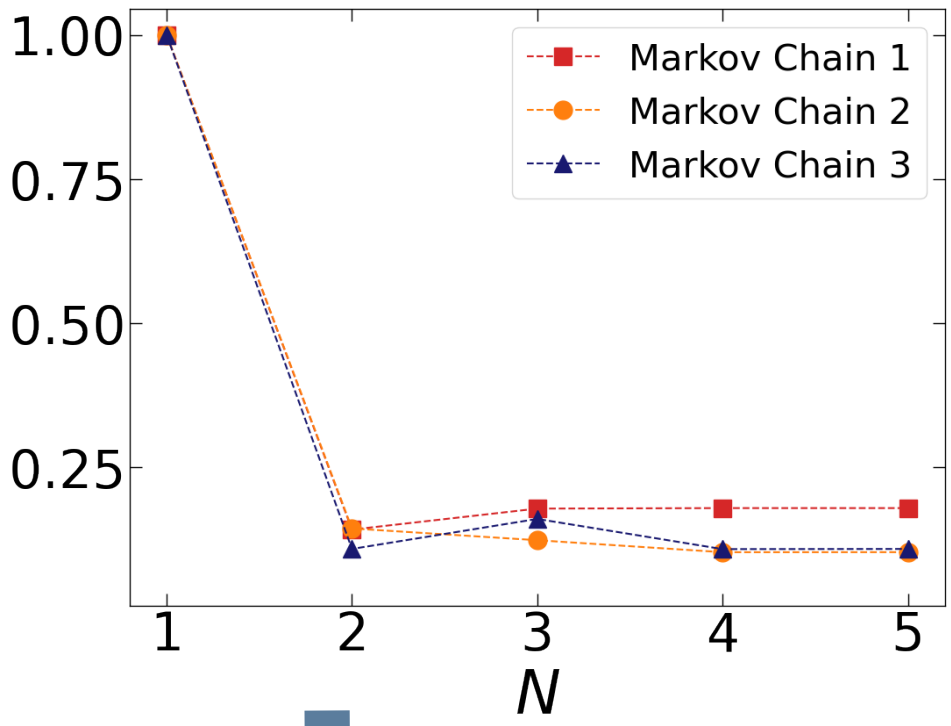


PROOF OF CONCEPT APPLICATION ON DWAVE

Transition path density



Path autocorrelation function



The quantum computer is reset in a linear superposition of states at each call. No autocorrelation!

Can this cross fertilization work the other direction?

Heavy quark diffusion in a QGP

Heavy quark bound states in a quark–gluon plasma: Dissociation and recombination

Jean-Paul Blaizot [a], Davide De Boni [b,d], Pietro Faccioli [d,e], Giovanni Garberoglio [c,e]

EFFECTIVE STOCHASTIC DYNAMICS

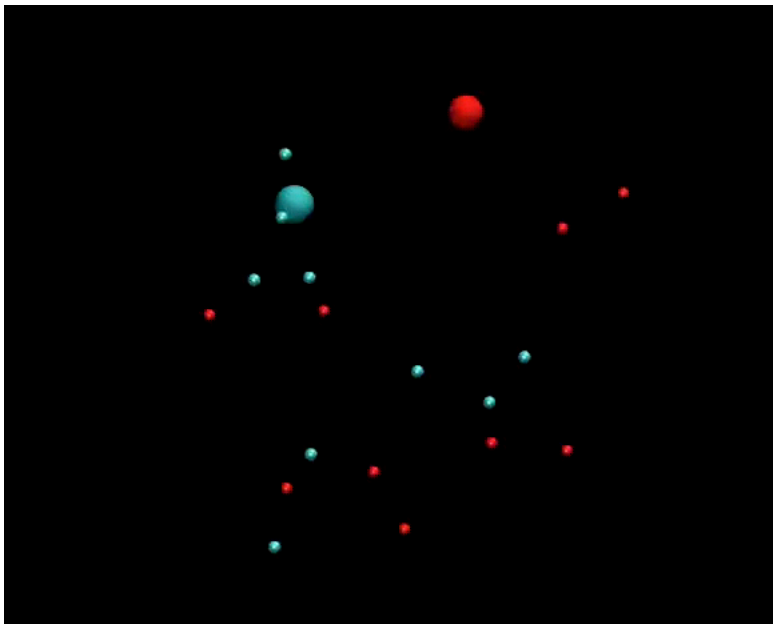
Model: NR relativistic particles coupled to an abelian plasma of fermions and gauge fields at finite temperature. After integrating out the gauge fields:

$$P(\boldsymbol{Q}_f, t_f \,|\, \boldsymbol{Q}_i, t_i) = \int_{\mathcal{C}} D\boldsymbol{Q} \int_{\mathcal{C}} D(\bar{\psi}, \psi)\, \mathrm{e}^{\mathrm{i}\, S[\boldsymbol{Q}, \psi, \bar{\psi}]}\,,$$

After integrating out the fermions and making the Ohmic approximation => **Effective Generalized Langevin**

$$M\,\ddot{\mathbf{R}} = -M\boldsymbol{\gamma}(\mathbf{R})\cdot\dot{\mathbf{R}} + \mathbf{F}(\mathbf{R}) + \boldsymbol{\xi}(\mathbf{R},t)\,,$$

$$\langle\,\xi_{i'}(\mathbf{R},t)\,\rangle = 0, \qquad \langle\,\xi_{k'}(\mathbf{R},t)\,\xi_{m'}(\mathbf{R},t')\,\rangle = \boldsymbol{\lambda}_{k'm'}(\mathbf{R})\,\delta(t-t')\,.$$



QGP plasma polarization induced by heavy fermions

LESSONS I HAVE LEARNED ALONG THE WAY

(…so far…)

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

However, working **multidisciplinary** collaborations requires a new paradigm

Technological transfer can boost research and help advance Science

Long journey, many fantastic collaborations…

Giovanni Spagnolli, Tania Massignan, Andrea Astolfi, Silvia Biggi, Paolo Brunelli, Michela Libergoli, **Simone Orioli**, Alan Ianeselli, Giulia Maietta, Marta Rigoli, Alberto Boldrini, Luca Terruzzi, Laura Tosatto, **Benedetta Mennucci,** Luise Linsenmeier, Beatrice Vignoli, Gianluca Petris, Maria Pennuto, Graziano Guella, Giovanni Piccoli, Marco Canossa, **Patrick Wintrode, Anne Gershenson,** Hermann Altmeppen, Graziano Lolli, Ben Schuler, Stefano Biressi, Roberto Covino, Cristian Micheletti, Jesùs R. Requena, Ines Mancini, Maria Letizia Barreca, Giovanni Garberoglio, Francesco Pederiva, Marcello Sega, **Silvio A Beccara, Henri Orland.**

Emiliano Biasini
CIBIO U. Trento