From Quarks to Drugs

Pietro Faccioli
A SCIENTIFIC JOURNEY
Prologue: proteins are complex many-body systems.
Challenge:
Integrate $\sim 10^6$ coupled Newton-type equations looking for extremely rare events
RARE EVENT PROBLEMS

MD

Protein folding

ms  s  minutes
MD YIELDS CORRECT PROTEIN NATIVE STATES

Anton supercomputer (DES Research)

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, Stefano Piana, Ron O. Dror, David E. Shaw

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Our research group has developed a special-purpose, high-speed molecular dynamics (MD) supercomputer, Anton, with the specific goal of studying fundamental questions in biophysics and biotechnology. Here, we describe our recent application of Anton to investigate the fundamental question of how proteins fold: What are the fastest pathways and intermediates for protein folding? In this study, we use the MD supercomputer to simulate the folding of 12 proteins representing all three major structural classes, spontaneously and repeatedly fold to their experimentally determined native structures. Early in the folding process, the protein backbone topology, and stability of the native structure appear in an order highly correlated with their propensity to form in the unfolded state.

The melting temperature, at which both folding and unfolding are observed, was always lower in the simulation than in experiment. In the case of the folded state, the RMSD was found to be constant at 2 Å, with the exception of the folding of ubiquitin. The high melting temperature of ubiquitin is a consequence of the large number of solvent molecules that must be expelled to form the native structure. For all 12 proteins that folded in simulation, calculations of the melting temperature were consistent with the experimentally determined values.

In our simulations, all of which used a single energy function, the proteins, representing all three major structural classes, spontaneously fold to their experimentally determined native structures. Early in the folding process, the protein backbone topology and stability of the native structure appear in an order highly correlated with their propensity to form in the unfolded state.
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

U

R
PHASE DIAGRAM

Hadrons

- deconfined phase
- hadronic phase
- CFL phase

Proteins

- molten globule phase
- folded phase
- coil phase
- denaturant concentration (urea)
PHASE 1: MATHEMATICAL FORMALISM & HIGH PERFORMANCE COMPUTING
PATH INTEGRAL REPRESENTATION

Hamilton’s equations

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

Langevin equations

\[ M\ddot{r}_i = -\nabla_i U(R) - \gamma_i \dot{r}_i + \eta_i(t) \]
A USEFUL ANALOGY

Thermal activation

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

Quantum tunneling

\[ K_E(x_f, t|x_i) = \int_{x_i}^{x_f} \mathcal{D}q \ e^{-\frac{1}{\hbar} \int_0^t d\tau (\frac{M}{2} \dot{q}^2 + U(q))} \]
$t_{TPT} \sim \tau_0 \log \left[ \log \left( \frac{t_{MFPT}}{\tau_0} \right) \right]$
All atom 3D structure of the native state are given in input, not predicted.
VARIATIONAL APPROACHES TO TRANSITION PATH SAMPLING

Dominant Reaction Pathways

(2005)

Dominant Pathways in Protein Folding

(2006)

Quantitative Protein Dynamics from Dominant Folding Pathways

(2012)

Dominant folding pathways of a WW domain

Silvio a Beccara*, Tatjana škrbić*, Roberto Covino*, and Pietro Facioli**

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

(2015)

Bias Functional Approach

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

(2017)

Self Consistent Path Sampling

Self-consistent calculation of protein folding pathways

S. Orioli, S. a Beccara, and P. Facioli*
between the Gibbs distribution and the SCR estimate forward and backward-combinators, as in Eq. (A3). Introducing the distribution

\[ P^{(t)}(x,t) \equiv \int dx P^{(t)}(x,t|x,0) \rho(x), \]

the density in Eq. (22) reads

\[ m_{\text{SCR}}(x) = \frac{1}{\beta - \tau} \int_0^\tau dt \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

Using the detailed balance condition, we find \( P^{(t)} = e^{-\beta H(x)} \frac{1}{Z} \mathcal{Q}^{(t)}(x,t; \beta) P^{(t)} \). Then, inserting this into Eq. (22), we find

\[ m_{\text{SCR}}(x) \approx e^{-\beta H(x)} \frac{\mathcal{Q}^{(t)}(x,t; \beta)}{Z} \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

Finally, recalling that \( \mathcal{Q}^{(t)}(x,t; \beta) \) and \( \mathcal{Q}^{(t)}(x,t; \beta - \tau) \) are π-time independent in the SCR and using Eqs. (17) and (18), we recover a fundamental result of TPT [cf. Eq. (A5) and Appendix A],

\[ m_{\text{SCR}}(x) \approx e^{-\beta H(x)} \frac{\mathcal{Q}^{(t)}(x,t; \beta)}{Z} (1 - \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t)). \]

Within the same framework, it is possible to evaluate the effective current in the SCR in complete analogy with Eq. (22),

\[ J_{\text{SCR}}(x) = -\frac{\partial}{\partial x} \int_0^\tau dt \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t) \times \left[ \frac{\partial}{\partial x} + \beta T(x) \right] P^{(t)}(x,t). \]

\[ \mathcal{L}_f(x) \approx \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta) - \frac{1}{2} \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

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 path integral (15), in which the UV cutoff has been lowered from \( \Omega \) to \( \Omega / 2 \). Equivalently, the path integral is discretized according to a larger elementary time step, \( \Delta t \to \Delta t/2 \).

In these expressions, the symbol \( N \) denotes the fact that the path integral is discretized according to an elementary time step \( \Delta t \) and we have suppressed the subscript \( \tau \), in the path. It can be shown that the proportionality factor between \( \mathcal{G}(i,j) \) and \( \mathcal{L}_f(i,j) \) and \( \mathcal{S}(i,j) \).

\[ \mathcal{S}(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \]

\[ \mathcal{L}_f(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

Notice that each term in the perturbative expansion (25) generates a new vertex, with an increasing power of the \( x_v(x) \) field. The couplings to the flat modes depend implicitly on the time \( \tau \), through the slow modes \( x_v(x) \).

By Wigner's scheme, each term in the series (26) can be related to a Feynman graph with vertices given by (26) and propagators given by (see appendix A).

\[ \mathcal{L}_f(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

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

\[ \mathcal{S}(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

II. SELF-CONSISTENT PATH SAMPLING

Let us introduce our new algorithm, which provides major improvement with respect to the MCMC and IFM schemes discussed in Sec. II. 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 (22). We introduce two dumb auxiliary variables \( x_v(x) \) and \( x_v(x) \) into this path integral by means of appropriate functional Dicke-dressed path integral representation:

\[ \mathcal{S}(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

\[ \mathcal{L}_f(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

\[ \mathcal{S}(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]

\[ \mathcal{L}_f(i,j) = \sum_{k=1}^N \mathcal{G}(i,k) \mathcal{Q}(k,j) \frac{\partial}{\partial x} \left[ (1 - \mathcal{Q}^{(t)}(x,t; \beta) \frac{\partial}{\partial x} \right] \mathcal{Q}^{(t)}(x,t; \beta - \tau) P^{(t)}(x,t). \]
VALIDATING SCPS AGAINST MD

Protein folding

MD

ms

s

minutes
VALIDATING SCPS AGAINST MD
VENTURING INTO THE BIO-ZONE

Our Simulations

MD

ms s minutes hours
HUGE COMPUTATIONAL GAIN

Using top all-purpose supercomputers

Using top special-purpose supercomputer
PHASE 2: VALIDATION

Experiment

Theory

\[ L = \frac{1}{2} \sum \sum_{\alpha \beta} \left( i \hbar \gamma_{\alpha \beta} \right) \left( \psi^{\dagger} \gamma^\mu \partial_\mu \psi - m_\alpha \psi^{\dagger} \gamma^\mu \gamma^\nu \partial_\mu \psi^{\dagger} \gamma^\nu \psi \right) \]

where

\[ \gamma^0 = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix}, \quad \gamma^1 = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}, \quad \gamma^2 = \begin{pmatrix} 0 & -i \\ i & 0 \end{pmatrix}, \quad \gamma^3 = \begin{pmatrix} 1 & 0 \\ 0 & -1 \end{pmatrix} \]

and

\[ D^\alpha = \partial^\alpha + \gamma^\alpha A_{\alpha} \]

Thus, it is...
VALIDATION AGAINST EXPERIMENT

Challenge:
Most available techniques provide only indirect probes, we seek for direct validation.
TIME-DEPENDENT LINEAR SPECTROSCOPY

Challenge:

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

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Ground state

One exciton
\[ \hat{\rho}(t) = e^{\frac{i}{\hbar} \hat{H} t} \hat{\rho}(0) \ e^{-\frac{i}{\hbar} \hat{H} t} \]
Using QFT we get rid of the multiple time issue:

\[ \phi'(\mathbf{x}, t) \]

Just like anti-particles

\[ \phi''(\mathbf{x}, t) \]

One “relativistic” field doublet but just one time
Molecular Quantum Field Theory*

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

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

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

\[
S_{S}[\psi, \bar{\psi}] = \sum_{n,m} \int_0^t d\tau \bar{\psi}_n(\tau) (i\hbar \delta_t - h^0_{nm}) \psi_m(\tau)
\]

\[
S_{int}[q, \psi, \bar{\psi}] = \sum_{nm} \sum_i \int_0^t d\tau \ f_{nm}^i \bar{\psi}_n \psi_m \delta q_i
\]
SOLVING MQFT: AN ARSENAL OF METHODS

- Perturbation Theory
  - PRB 2012, PRB 2013, PRB 2016

- Quantum MC (for real time)
  - PRB 2016

- Renorm. Group & Eff. Field Theory
  - PRB 2013, JCP 2016
EXAMPLES OF DIRECT COMPARISON WITH EXPERIMENTS

Time resolved near UV CD*

Linear absorption spectrum

Experimental
Calculated

Normalized Absorption

Frequency (cm$^{-1}$)

Microscopic Calculation of Absorption Spectra of Macromolecules: an Analytic Approach

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

Alan Lanesoni, Simone Orabà, Giovanni Spagnoli, Pietro Facciotti, Lorenzo Capellina, Sandro Juraswich, and Benedetta Meninucci

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* with B. Mennucci’s Lab (U. Pisa)
PHASE 3: EXPLOITATION IN MOLECULAR BIOLOGY
EXPLORING BIOLOGICAL PROCESSES

Serpin latency transition at atomic resolution

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

PLOS PATHOGY

RESEARCH ARTICLE

Full atomistic model of prion structure and conversion

All-Atom Simulation of the HET-s Prion Replication

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

DNA -> mRNA -> Ribosome -> Protein folding -> Protein function

RNA silencing

Eliminating protein from genome

Suppressing transcription

Suppressing folding

Impairing function

patent file # 102018000007535 (with E. Biasini)
PHARMACOLOGICAL PROTEIN INACTIVATION BY FOLDING INTERMEDIATE TARGETING

Unfolded state → $l_1$ ↔ $l_2$ → Native state

Drug

Unfolded proteins → Degradation
Virtual screening on folding Intermediate

Biochemical Validation

PPI-FIT PIPELINE
Virtual screening on folding Intermediate Folding pathway characterization

**PPI-FIT PIPELINE**

Biochemical Validation with L. Barreca’s Lab
Inactivation of Cellular Prion protein

Recent computational advancements in the simulation of biochemical processes allow investigating the mechanisms involved in protein regulation with realistic physics-based models, at an atomistic level of resolution. These techniques allowed us to design a drug discovery approach, named Pharmacological Protein Inactivation by Folding Intermediate Targeting (PPI-FIT), based on the rationale of negatively regulating protein levels by targeting folding intermediates. Here, PPI-FIT was tested for the first time on the cellular prion protein (PrP), a cell surface glycoprotein playing a key role in fatal and transmissible neurodegenerative pathologies known as prion diseases. We predicted the all-atom structure of an intermediate appearing along the folding pathway of PrP and identified four different small molecule ligands for this conformer, all capable of selectively lowering the load of the protein by promoting its degradation. Our data support the notion that the level of target proteins could be modulated by acting on their folding pathways, implying a previously unappreciated role for folding intermediates in the biological regulation of protein expression.

**ARTICLE**

Pharmacological inactivation of the prion protein by targeting a folding intermediate

**COMMUNICATIONS BIOLOGY**
Technology Transfer Initiative
Joining Forces against COVID-19

Maria Letizia Barreca
Emiliano Biasini
Pietro Faccioli
Graziano Lolli

Lidia Pieri
Giovanni Spagnolli
Alberto Boldrini
Tania Massignan

Luca Terruzzi
Andrea Astolfi

30,000 cores in 8 data centers
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
Out of 9000 candidates, we found 35 molecules binding in-silico the intermediate. Validation experiments on cellular bio-assays are ongoing.
DOSE-DEPENDENT RESPONSE

Cell-based validation of candidate hits.

µM, not shown). Collectively, these results indicate that different experiments (n...}

...entry for a pseudotyped retroviral vector exposing the SARS-CoV-2 spike protein.

The ability of the selected compounds to lower the expression of ACE2 translates in a reduced cellular...}

...inhibited retroviral transduction in a dose-dependent fashion, at concentrations similar to those at which...}

...Vero cells incubated with each of the four candidate compounds at different concentrations were trans...}

...Statistically significant differences are indicated by the asterisk (* p < 0.05).
Antiviral activity against live SARS-CoV-2

Antiviral activity displayed by Artefenomel was not due to cytotoxicity. None of the concentrations induced CPE at a concentration of 11 µM. Beclabuvir also completely prevented the virus-antiviral activity displayed by Artefenomel. Artefenomel (expressed as IC<sub>50</sub>) values were generated with Graphpad Prism in the case of Artefenomel. IC<sub>50</sub> and CC<sub>50</sub> values are shown as greater values were generated with Graphpad Prism in the case of Artefenomel. IC<sub>50</sub> coefficients of variation (C.V.) are effectively inhibit virus replication. However, selectively decreasing the expression of ACE2 is a host target protein could be a di...
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!
The least biased trajectories were projected on two graphs plotting the RMSD of each relevant region (residues 468-498 or C-terminal tail) against the RMSD of the corresponding docking site. These analyses revealed that the pocket 1 is present in a single trajectory, while the pocket 2 is predicted to appear in 9 different trajectories.

In Silico Identification of Potential Binders of ACE2 Intermediate

The identification of potential ACE2 folding intermediate ligands was pursued by employing a drug repositioning strategy. We built a unique collection of 9187 compounds by combining libraries of drugs approved by the U.S. Food and Drug Administration (FDA) and molecules at different stages of currently ongoing clinical trials (see Material and Methods). The chemical collection was screened against the two identified pockets by following a consensus virtual screening workflow (Figure 7). Two different docking software, Glide\textsuperscript{22} and LeadIT\textsuperscript{24}, were employed in parallel to predict the binding affinity of each compound to the ACE2 folding intermediate pockets. Only compounds showing promising predicted affinity (i.e. Glide	extsuperscript{ds} \leq -6 \text{kcal/mol}; LeadIT HYDE \text{aff} \leq 50 \mu\text{M}) in both docking protocols were submitted to a third docking round based on AutoDock\textsuperscript{25}. This process identified two consensus sets (AD	extsuperscript{ALBE} \leq -6 \text{kcal/mol}, AD	extsuperscript{NiC} \leq -6 \text{kcal/mol}), including 145 compounds for pocket 1 and 238 for pocket 2. The top scoring compounds from Glide (Glide	extsuperscript{ds} \leq -9 \text{kcal/mol}) and LeadIT (HYDE \text{aff} \leq 5 \mu\text{M}) were also added to these sets. Finally, a visual inspection of binding mode and chemical similarity annotation for each ligand allowed the selection of 14 virtual hits for pocket 1 and additional 21 for pocket 2 (Supp. Table 2).
Molecular Biology
(functional role of folding intermediates?)

ZEFIR MISSION*

Quantum Computing + AI

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Dominant Reaction Pathways by Quantum Computing

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