Ligand induced protein stabilization and enahanced molecular dynamics sampling techniques

Timo Schäfer*, Andreas C. Joerger+, John Spencer$, Friederike Schmid* and Giovanni Settanni*
*Physics Department, J.-Gutenberg University Mainz, + Institute of Pharmaceutical Chemistry, J.W.-Goethe University Frankfurt, $Dept. of Chemistry, University of Sussex

Simulations of p53 cancer mutants and stabilization by ligand binding

The tumor suppressor protein p53 is involved in several processes protecting the human genome, including activation of DNA repair mechanisms or induction of apoptosis (cell death) in case of extensive DNA damage. Mutations of this protein can often result in cancer and, indeed, mutations in this protein occur in half of the diagnosed cancers.
Simulations help rationalize the effect of mutations by linking the root mean squared fluctuation to the experimentally measured unfolding temperature.

Codon 220 mutation	Average RMSF (Å)	Tm (°C)
Native structure		
WT	1.46	51.5
Y220H	1.56	45.1
Y220C	1.61	43.8
Y220N	1.64	39.9
Y220S	1.67	39.4
Ligand complexes		
Y220C-PK9323	1.35	
Y220S-PK9301	1.42	
Y220S-PK9323	1.58	

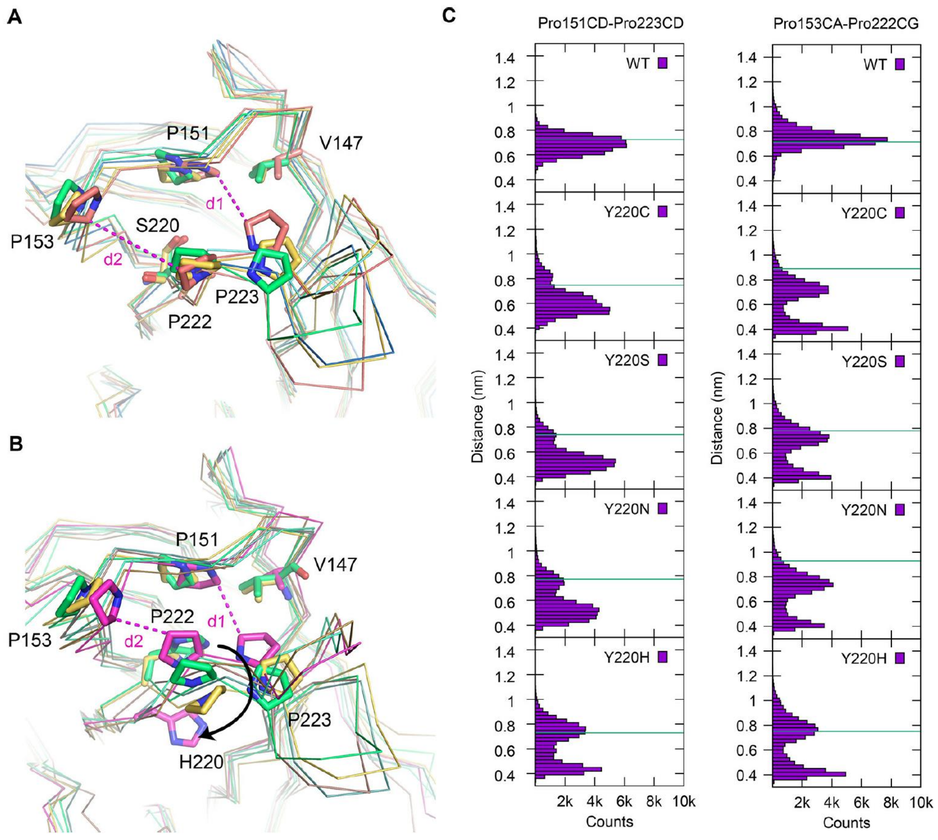

Fig. 1. Conformations of the p53 mutation site from MD simulations of the mutants Y220S (A) and Y220H (B) superimposed over the crystal structure (green). The distances d1 and d2 help measure the size of the mutation-induced pocket. (C) histograms of the distances in the various mutants highlighting the presence of open and closed states. Adapted from ref. [0], Bauer et al. ©2020 licensed under CC-BY.

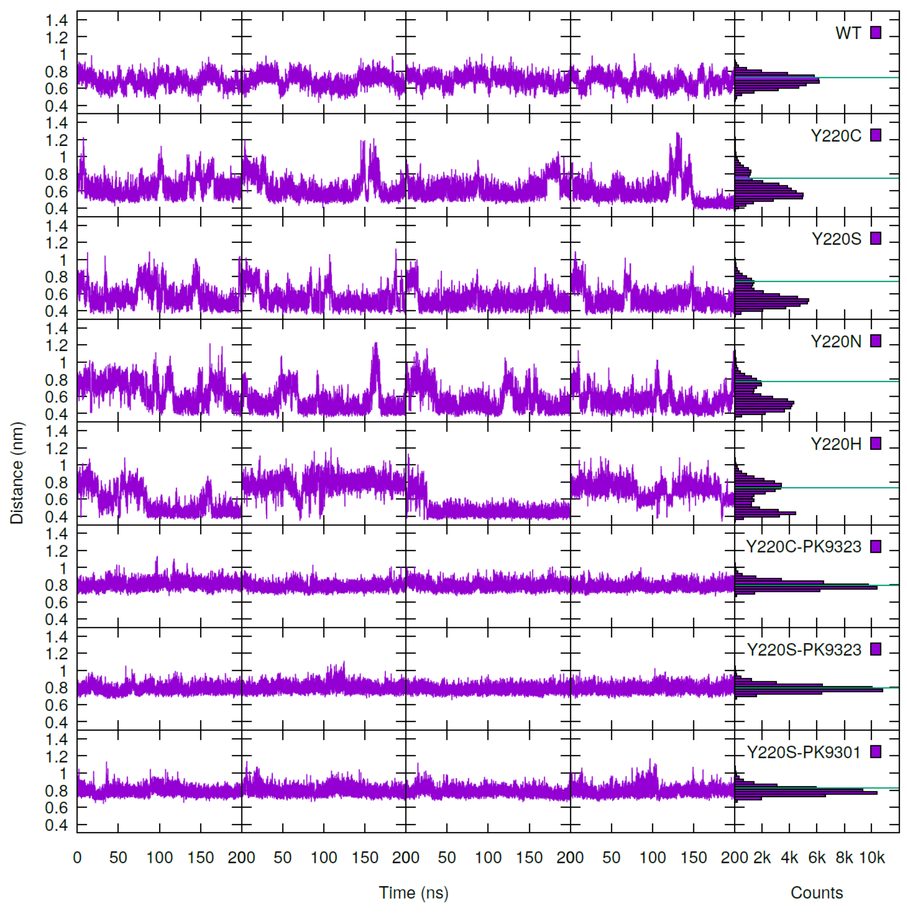

Fig. 2. Time series and distribution of the d1 distance in fig.1 in the various mutants and effect of the presence of ligands, which dramatically reduce fluctuations when bound to the pocket. Adapted from ref. [0], Bauer et al. ©2020 licensed under CC-BY.

References
[0] Matthias R. Bauer, et al. ACS Chem. Biol. 2020, 15, 3, 657–668
https://doi.org/10.1021/acschembio.9b00748

Data reweighting in Metadynamics simulations

In metadynamics simulations a time dependent bias potential is added to the energy of the system in order to enhance the sampling along selected, and hopefully relevant, collective variables(CV).

$$V(\boldsymbol{s}(\boldsymbol{r}),t) = \sum_{t'=\Delta t,2\Delta t,\ldots}^{t} W e^{-\sum_i^d (s_i(\boldsymbol{r})-s_i(\boldsymbol{r}(t')))^2/2\sigma_i^2} = \sum_{t'=\Delta t,2\Delta t,\ldots}^{t} g_{t'}(\boldsymbol{r},\boldsymbol{s}(t'))$$

The underlying unbiased free energy landscape as a function of the CV can then be approximated by negative bias potential:

$$F(s) \approx -\frac{\gamma}{\gamma-1}V(s,t) + c(t)$$

The conformations sampled along the biased simulations can be used to estimate unbiased averages via a reweighting procedure:

$$< A >_0 = < Aw >_\mathrm{b} \; / \; < w >_\mathrm{b}$$

One well-established reweighting scheme was proposed by Tiwari and Parrinello [3]:

$$w^{tw}(\boldsymbol{r},t) = e^{\beta V(\boldsymbol{s}(\boldsymbol{r}),t)} \frac{\int d\boldsymbol{s}}{\int d\boldsymbol{s} e^{\beta V(\boldsymbol{s},t)}} = e^{\beta V(\boldsymbol{s}(\boldsymbol{r}),t)} \frac{1}{\langle e^{\beta V(\boldsymbol{s},t)} \rangle_{\boldsymbol{s}}} \quad (1)$$

In [5] we propose a new reweighting scheme

$$w^{bex}(\boldsymbol{r},t) \propto e^{\beta V'(\boldsymbol{s}(\boldsymbol{r}),t)} = e^{\beta(V(\boldsymbol{s}(\boldsymbol{r}),t)-V_a(t))} = e^{\beta V(\boldsymbol{s}(\boldsymbol{r}),t)} \frac{1}{e^{\beta \langle V(\boldsymbol{s},t) \rangle_{\boldsymbol{s}}}}. \quad (2)$$

In practice the difference between the reweighting scheme in eq. (1) and our proposal in eq. (2) is in the normalization of the exponential weight.

This implies that although eq. (1) may be more accurate on long time scales it converges more slowly than eq. (2).

It can also be shown that eq. (2) in the case of standard metadynamics is mathematically equivalent to the scheme presented in [2] although the histogram-based implementation of the latter introduces variations.

Results

To test the various reweighting schemes we preform metadynamics simulations in different settings and evaluate F(s) from the histogram of the reweighted conformations.

Unidimensional double-well potential

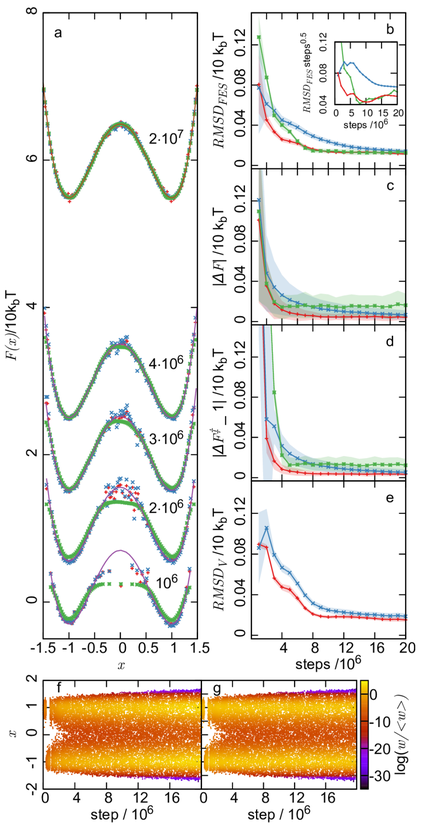

Fig.3 Estimated FES and deviations from reference for the proposed balanced exponential ref.[5] (red) and ref. [3] (blue) reweighting schemes as well as negative bias (green). Adapted with permission from ref. [5], ©2020 ACS

Standard Metadynamics of Alanine dipeptide CV=(φ,ψ)

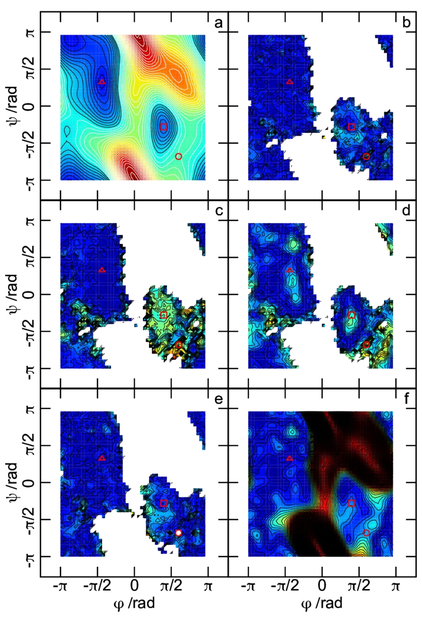

Fig.4 Estimated FES, (a) Reference, (b) balanced exponential [5], (c) ref. [3], (d) ref. [4], (e) ref. [2], (f) negative bias. Adapted with permission from ref. [5], ©2020 ACS

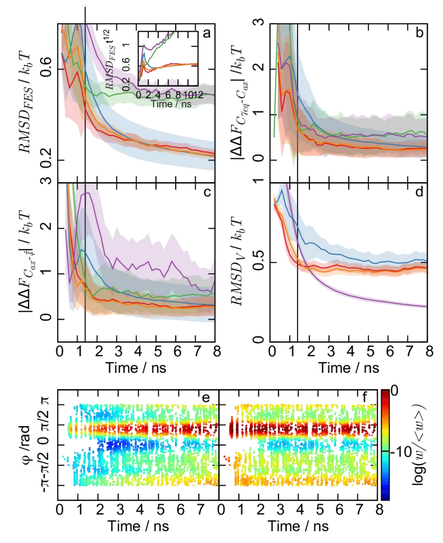

Fig.5 Deviation from reference. Color scheme as in Fig.3 with, in addition, ref. [4] (purple), ref. [2] (orange). Adapted with permission from ref. [5], ©2020 ACS

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