***eLife’s* transparent reporting form**

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**Sample-size estimation**

* You should state whether an appropriate sample size was computed when the study was being designed
* You should state the statistical method of sample size computation and any required assumptions
* If no explicit power analysis was used, you should describe how you decided what sample (replicate) size (number) to use

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

**All the results reported in the paper are from molecular dynamics simulations.**

The length of the standard simulations that we ran is reported in Table 1, while the length of the PTmetaD is reported in the Methods section, *Metadynamics simulations details* subsection.

Since the sampling currently accessible on a supercomputer via unbiased simulations is not sufficient to sample a sufficient number of spontaneous transition from the active to the Src-like inactive conformation, we ran enhanced sampling simulations by means of the PTmetaD algorithm.

The length of the PTmetaD was determined by a strict convergence criterion as described in the Methods section *Metadynamics simulations details* subsection.

**Replicates**

* You should report how often each experiment was performed
* You should include a definition of biological versus technical replication
* The data obtained should be provided and sufficient information should be provided to indicate the number of independent biological and/or technical replicates
* If you encountered any outliers, you should describe how these were handled
* Criteria for exclusion/inclusion of data should be clearly stated
* High-throughput sequence data should be uploaded before submission, with a private link for reviewers provided (these are available from both GEO and ArrayExpress)

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PTmetaD is an algorithm that uses multiple replicas of the system that exchange according to a Metropolis criterium. What is more, a number of standard MD simulations of the systems were run.

**Statistical reporting**

* Statistical analysis methods should be described and justified
* Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
* For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
* Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

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The free energy landscapes were obtained by means of a multiple replica algorithm. The statistical error on the sampling was estimated according to the best practice approach accepted by the community, as discussed in Materials and Methods.

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

**Group allocation**

* Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
* Indicate if masking was used during group allocation, data collection and/or data analysis

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn’t apply to your submission:

Not applicable to our study.

**Additional data files (“source data”)**

* We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
* Where provided, these should be in the most useful format, and they can be uploaded as “Source data” files linked to a main figure or table
* Include model definition files including the full list of parameters used
* Include code used for data analysis (e.g., R, MatLab)
* Avoid stating that data files are “available upon request”

Please indicate the figures or tables for which source data files have been provided:

System initial coordinates and topologies, MD engine input files, as well as Plumed and PDB files required for the calculation of the reported free energy surfaces have been deposited to our local Github repository and by the time of the publication, they will have also been deposited to the public repository PLUMED-NEST.

<https://github.com/yiannisgaldadas/Gervasio-Protein-Dynamics/tree/master/EGFR>