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Last updated by author(s):	Aug 17, 2020

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, seeAuthors & Referees and theEditorial Policy Checklist.

Statistics	
For all statistical analys	es, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.
n/a Confirmed	
The exact sam	ple size (n) for each experimental group/condition, given as a discrete number and unit of measurement
A statement o	on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
	test(s) used AND whether they are one- or two-sided ests should be described solely by name; describe more complex techniques in the Methods section.
A description	of all covariates tested
A description	of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
X	ion of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
	hesis testing, the test statistic (e.g. F , t , r) with confidence intervals, effect sizes, degrees of freedom and P value noted exact values whenever suitable.
For Bayesian a	analysis, information on the choice of priors and Markov chain Monte Carlo settings
For hierarchic	al and complex designs, identification of the appropriate level for tests and full reporting of outcomes
Estimates of e	ffect sizes (e.g. Cohen's d , Pearson's r), indicating how they were calculated
	Our web collection on <u>statistics for biologists</u> contains articles on many of the points above.
Software and c	ode
Policy information abou	ut <u>availability of computer code</u>
Data collection	amber18, gromacs2019.2, plumed2.5
Data analysis	cpptraj, python, pyemma2
	om algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.
Data	
Accession codes, uniA list of figures that	nclude a <u>data availability statement</u> . This statement should provide the following information, where applicable: ique identifiers, or web links for publicly available datasets have associated raw data restrictions on data availability
All data that support the	finding of the study are available from the corrosponding author upon request.
Field-speci	fic reporting
Please select the one b	elow that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.
x Life sciences	Behavioural & social sciences Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see $\underline{\mathsf{nature}.\mathsf{com}/\mathsf{documents}/\mathsf{nr}-\mathsf{reporting}-\mathsf{summary}-\mathsf{flat}.\mathsf{pdf}}$

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.		
Sample size	Data were generated with state-of-the-art enhanced sampling techniques and were analyzed by Markov models.	
Data exclusions	No data were excluded.	
Replication	The Bayesian statistics inherent to the Markov models comprise fifty repetitions guaranteeing statistical significance.	
Randomization	The statistical procedure repeated fifty times contains different clustering of results each time.	
Blinding	Blinding is not applicable with computer experiments.	

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

terials & experimental systems	Methods
Involved in the study	n/a Involved in the study
Antibodies	ChIP-seq
Eukaryotic cell lines	Flow cytometry
Palaeontology	MRI-based neuroimaging
Animals and other organisms	•
Human research participants	
Clinical data	
	Involved in the study Antibodies Eukaryotic cell lines Palaeontology Animals and other organisms Human research participants