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LETTER TO THE EDITOR

Molecular dynamics of α-helical structure: poly-L-glutamic acid

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1. Introduction

The protein molecule consists of the blocks of regular structures called standard structural motifs or super-secondary structures. A discovery of α-helical conformation as a basic structure of the α-keratin proteins by Pauling and Corey (1951) opened the way for understanding the world of protein structures. Furthermore, at the end of XX century such unique motifs well known as βαβ 'Rossmann fold', ββββ 'Greek key' and two helical 'αα-corner' have been discovered in the pioneering works (Efimov, 1984; Rao & Rossmann, 1973; Richardson, 1977). Subsequently, nearly twenty other standard motifs have been revealed (Efimov, 1993, 1997; Gordeev et al., 2010) based on the X-ray and NMR structure database the Protein Data Bank (Berman et al., 2002). The main amount of the 3D-structural data is related to the crystal state where protein molecules are fixed rather tightly. Nowadays, there are a few different approaches, such as nuclear magnetic resonance (NMR) and molecular dynamic simulation (MDS) which allow to study three-dimensional data for the protein molecule in solution (Rudnev et al., 2021). These approaches allow to study the structural behavior of protein in their native state in a water solution. Considering the complexity of the protein structure we have started a study the simple basic regular motif: short fragment of α-helix. In this communication we have investigated the dynamic properties of 16 residues fragment of poly-L-glutamic acid in a helical form in water solution. The atomic displacements of fluctuation modes have been inspected for only Cα-atoms of the peptide chain. As a result, we have found several very populated fluctuation modes which display distinctive dynamic Cα-atom shifts. The modes include two adjacent clusters of exited Cα-atoms which are localized approximately on one side of the helix. This is solely intrinsically feature of a single fragment of α-helix structure which suggests playing a key role in dynamics of whole proteins.

2. Description of method and data

2.1. Poly-L-glutamic acid model

A model of helical fragment of poly-L-glutamic acid (PGA) in a water solution is based on the well studied earlier experimental data (Bychkova et al., 1971; Chirgadze, & Brazhnikov, 1974). It includes 16 Glu residues placed in 4.5 turns of right-handed α-helix structure built with the data of Pauling and Corey (1951). In acidic water solution at pH 4.3 the helix-random coil transition of poly-L-glutamic acid occurs. The side groups of glutamic amino acid have p*K*a 4.3 in water, while NH2 and COOH of the N- and C-terminal groups have p*K*a 9.7 and 2.2, respectively (Hunt & Spinney, 2006). It has been shown experimentally that at pH 4.0 and 0.2 M NaCl about 85% of conformations exist in helical form (Bychkova et al., 1971). This means that in the model of helical form in acidic water solution at pH about 3.3 side carbonyl Glu groups are non-ionized, as COOH, and both Cα-terminal groups are ionized, as NH^{3+} and COO^{-}. Water medium consists of about seven water layers, and includes also 10 ions of Na and 10 ions of Cl. Total amount of atoms, including water molecules, is equals to 6610. The picture of initial model in solution after 500 ps of refinement and optimization is shown in Figure 1.

2.2. Molecular dynamics simulation

Molecular dynamics simulation has been performed in two stages:

- First trajectory T0: refinement of PGA model and dynamic relaxation, 0–25 ns;
- Four other independent trajectories T1–T4: fluctuation of PGA model. All of them started from the end of T0 and prolonged during 25 ns.

The result on the first trajectory T0 has been accompanied by calculation radius of inertia (Figure 2). It allows to see that relaxation process is is completed at about 12 ns. After this we can considered the fluctuations of trajectory T0 as the representative result. Four other trajectories T1–T4 were started after the end of T0. Consequently, they are presenting 100 ns of independent representative picture of dynamic fluctuations. Whole calculated system included helical fragment, water solution molecules, and ions of sodium and chlorine, total 20 ions. The computed cell size was equal to 37 × 37 × 49Å which is twice larger than the longest size of

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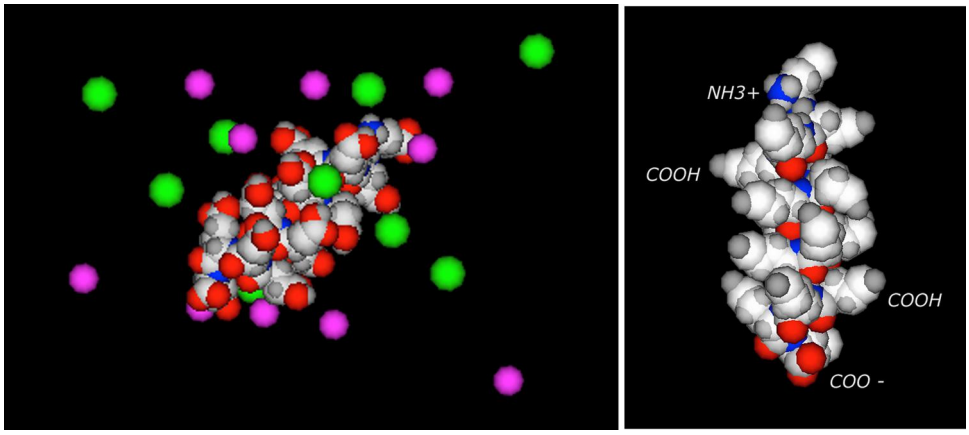

Figure 1. An initial model of fragment of α-helical poly-L-glutamic acid in water solution. *Left:* Expanded peptide model with standard colored atoms. Na and Cl^- ions are shown with magenta and green colors. Water solution molecules are not shown. Right: Peptide model with changed color of side COOH groups. Here the oxygen atoms are colored light gray to show they are more neutral in compare with the red oxygen atoms of peptide groups and charged carboxyl of C-terminal end.

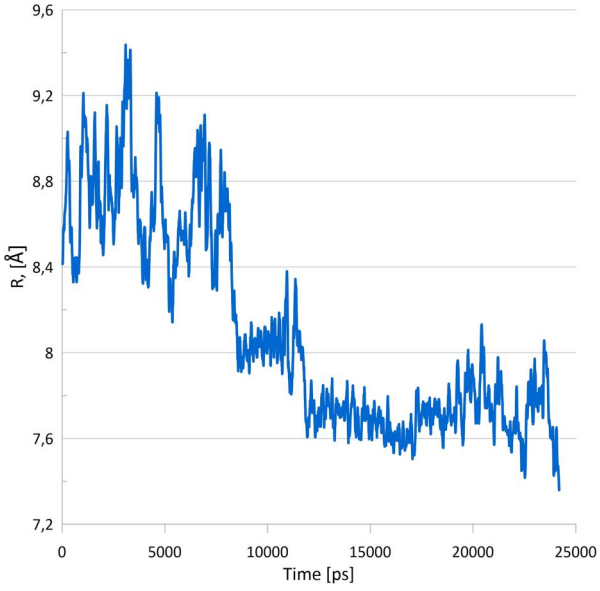

Figure 2. Time dependence of radius of inertia during relaxation.

the helix. Thus, we can consider our experiment as a 'full atomic molecular dynamic simulation' of the peptide helix with the water solution. Recording the macroscopic quantities, such as energy, temperature, pressure, has been done every 0.1 ps, and the output data for trajectory have been taken every 10ps. Deviation of the system has been controlled by the time dependance of PGA model radius of inertia for the first initial trajectory. In addition we have controlled the electrostatic Coulomb and non-polar Van der Waals potentials. The initial part of trajectories, 0–500 ps, corresponds to the structure refinement of the model with hydrogen atoms.

For analysis of conformational alterations we have used the original method of *time dependence of Cα-shifts* between two sequential pairs of frames (Chirgadze et al., 2021). Inspection of fluctuation of the Cα-chain has been carried out each integer time points, in nanoseconds. An absolute shifts of Cα-atom positions, that equals the module of atomic displacement, has been taken from two sequential time frames at 1.0 ns. During the dynamic process all the atoms are displaced. Besides, molecule model can be deformed and displaced as a whole. Thus, the *correct superposition* of two structures selected at different time requires to put them in the common internal coordinate system determined from tensor of moments of inertia. In this system the principal axes of both molecules are obtained by calculation the ellipsoid of inertia, and its origin is placed in the center of masses of the Cα-atoms. This important procedure has to be applied for each two sequential points of trajectory or at correct comparison of two dynamic structures in two points of time. Same procedure for alignment of two models was used as implemented in the PyMol program (Delano et al., 2000).

The calculations have been carried out with the help of programs based on the MDS standard software PUMA (Lemak & Balabaev, 1995, 1996) and modified by us PUMA–CUDA which is compatible with supercomputer code signs. Force field AMBER (Wang et al., 2000) was used as well as the program to generate the water medium model TIP3P (Mahoney & Jorgensen, 2000). The resulting trajectories of molecular dynamics were investigated by the Trajectory Analyzer of Molecular Dynamics TAMD (Likhachev & Balabaev, 2007, 2009; Likhachev et al., 2016).

3. Results and discussion

3.1. Molecular dynamics of poly-L-glutamic acid in solution

The fluctuation of the Cα-chain of α-helical poly-L-glutamic acid in the first trajectory T0 has been inspected along the whole dynamic trajectory. As an example, we present diagram of Cα-shifts for six frames in time period 1–7 ns (Figure 3). Here various fluctuation modes have been observed. Both ends of helix display large shifts. Along the internal part of helix three modes are clearly seen. These modes at time points 1–2, 3–4 and 4–5 ns display distinctive shifts along the internal part of helix. Two excited clusters of Cα-atoms have been observed along the polypeptide chain. Fluctuations occur inside of clusters 5–6–7 and 9–10–11 of Cα-atoms. However, the most interesting fluctuation mode are observed just after relaxation is completed, that is after 12 ns. Cα-atoms of two excited clusters

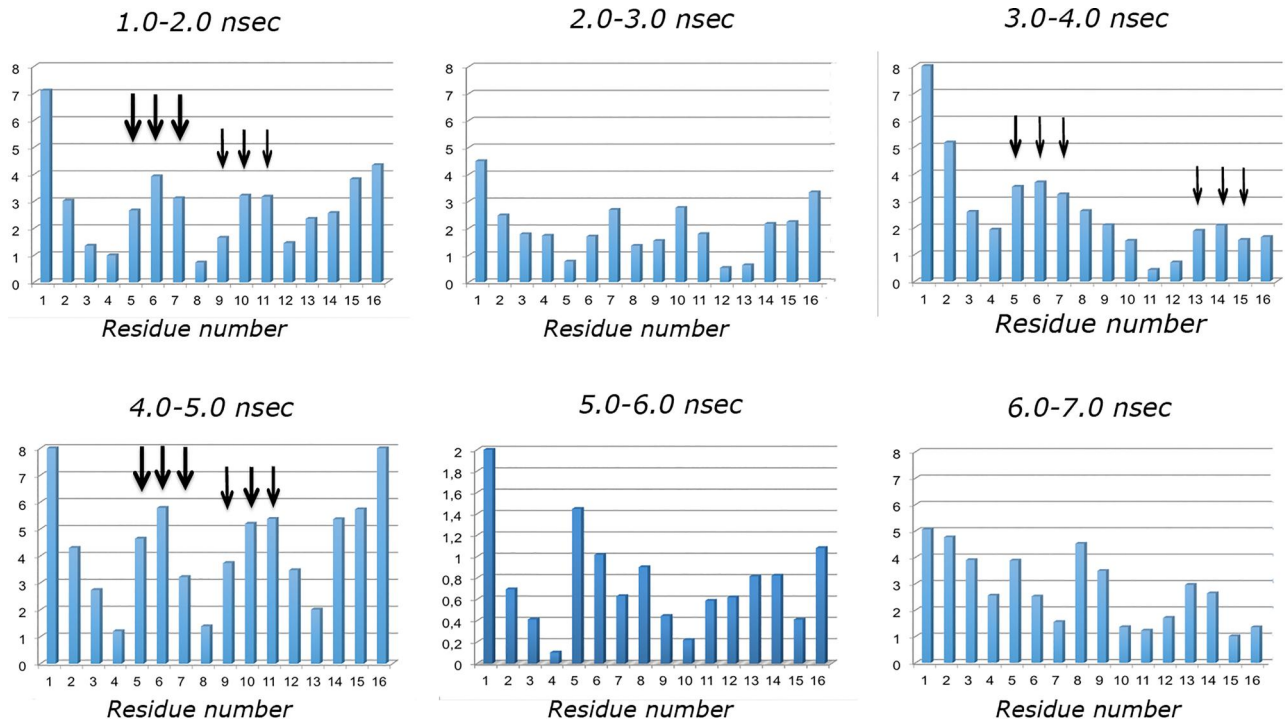

Figure 3. Dynamic fluctuation in helical poly-L-glutamic acid for time period 1.0–7.0 ns. Distinctive dynamic modes with two clusters of Cα-shifts are marked by black arrows. Absolute values of Cα-shifts are given in Å.

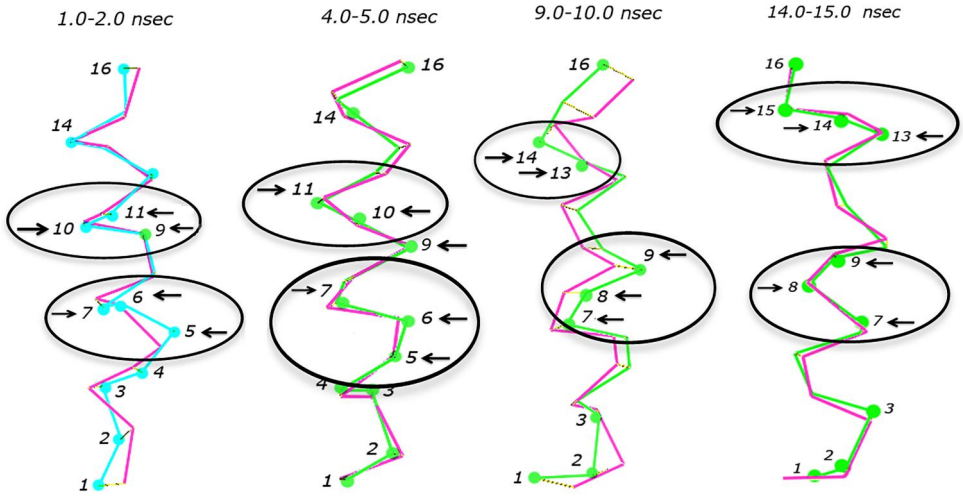

Figure 4. Examples of Cα-fluctuation modes of poly-L-glutamic acid helix observed in the first simulation run T0. Black arrows indicate the Cα-atoms with distinctive shifts. Two compared structures are marked with green and red colors. Clusters of excited atoms are marked as ovals.

were located at adjacent helical turns and related to the clusters 7–8–9 and 12–13–14. The corresponding displacements of Cα-atoms in the helix are shown in Figure 4.

3.2. Distinctive fluctuation modes of poly-L-glutamic acid in helical form

Confirmation of the main fluctuation feature has been obtained in four additional independent simulations, trajectories T1–T4. The distinctive fluctuation are presented in Table 1. For total time of 100 ns dynamic simulation we have observed about 20 very similar fluctuation modes in total 24 frames, that means 80%. They contains two clusters of Cα-atoms with distinctive shifts. There are two kinds of such modes: the first one includes clusters around Cα-atoms 6 and 10, and the second mode with clusters around Cα-atoms 8 and 13–14. The later fluctuation mode is more populated. In general, we should inspect all 100,000 calculated PGA frames. That requires a lot of work. We have checked the results in period 1.40–1.48 ns by decreasing an inspection step 10ps. As expected, we have observed 6 frames with distinctive fluctuation modes from total 9 frames, it means 67%. That confirms the stability of common dynamic feature for the results presented here.

Typical displacement of Cα-skeleton in this distinctive fluctuation mode is presented for time points 23–24 ns in

Figure 5. Here cluster 7–8–9 shows Cα-shifts perpendicular to helix axis, while cluster 13–14–15 displays shifts mainly along helix axis. Averaged shift of Cα-atoms in the clusters equals to 3.5 Å and those are larger in the terminal groups. It should be finally noted that N-terminal atoms 1–4 and C-terminal group 13–16 are displaced approximately along the helix but in opposite directions like stretching a spring.

Table 1. Dynamic fluctuation modes in four independent representative trajectories T1–T4 of helical poly-L-glutamic acid, each for 0–25 ns. The results have been obtained after completing the relaxation process.

Time of frame, ns	Cluster 1 helix turn 3	Cluster 2 helix turn 4	Cα-shifts, both clusters, Å (–) means no shifts			
	CLUSTERS	FOUND	TRAJECTORIES			
	Cluster 1	Cluster 2	T1	T2	T3	T4
00.0–01.0	8–9	14–15	3.5	–	1.0	8,0
01.0–02.0	7–8–9	13–14–15	6.0	1.0	–	1.0
02.0–03.0	7–8–9	13–14–15	–	2.5	0.6	2.0
03.0–04.0	7–8–9	12–13–14	3.5	3.5	0.8	–
04.0–05.0	7–8	13–14–15	2.0	1.0	1.0	1.5
05.0–06.0	8–9	14–15	3.0	8.0	0.5	2.3
06.0–07.0	8–9	14–15	–	1.5	1.0	–
07.0–08.0	7–8–9	12–13–14	–	1.0	1.5	3.5
08.0–09.0	8–9	14–15	8.0	1.5	2.0	2.0
09.0–10.0	7–8–9	12–13–14	2.0	1.0	1.8	3.0
10.0–11.0	7–8–9	12–13–14	1.5	8.0	0.8	2.0
11.0–12.0	7–8–9	13–14–15	1.5	1.0	1.0	2.5
12.0–13.0	7–8–9	13–14–15	1.0	1.0	2.5	3.0
13.0–14.0	7–8	13–14–15	1.0	–	–	6.0
14.0–15.0	7–8–9	13–14–15	–	1.0	1.0	2.5
15.0–16.0	7–8	13–14–15	1.0	2.5	1.0	3.5
16.0–17.0	7–8–9	13–14–15	1.5	9.0	3.0	–
17.0–18.0	7–8–9	13–14–15	2.0	–	–	3.0
19.0–20.0	7–8–9	13–14–15	2.0	1.0	1.0	0.8
20.0–21.0	7–8–9	13–14–15	2.5	–	1.0	1.3
21.0–22.0	7–8–9	12–13–14	1.5	–	–	3.5
22.0–23.0	7–8–9	12–13–14	3.0	1.5	2.5	–
23.0–24.0	7–8–9	12–13–14	2.0	1.5	1.5	1.5
24.0–25.0	7–8–9	12–13–14	–	1.5	1.5	1.2
Summary for repeated trajectories:						
Repeated trajectory:			**T1**	**T2**	**T3**	**T4**
Observed modes, from total 24 frames:			19	19	20	20
Amount of fluctuation modes, in %:			79	79	83	83

3.3. Modes of helical poly-L-glutamic acid in relation to α-helix by Pauling and Corey

Below we consider the distinctive fluctuation modes of poly-L-glutamic acid in relation to the basic α-helical structure by Pauling and Corey (1951, 1951). The fragment of the α-helix is presented in Figure 6. Non-integer number of Cα-atoms per turn in α-helix equals to 3.6. Peptide groups of the adjacent turns are bound with hydrogen bonds NH…O. They are connected by super-helical right-handed tracing lines which are inclined at about 30 degrees to helix axis. The dynamic fluctuation shifts of Cα-atoms in the clusters occurs mainly on one helix side as seen in Figure 6.

Before we discuss the parameters of fluctuation modes of poly-L-glutamic acid in solution we state that distinctive mode is an intrinsic feature of the helical structure. This mode appears continuously along the whole dynamic trajectory of the helical model of poly-L-glutamic acid in water medium. It includes two clusters of fluctuation groups of Cα-atoms which are on adjacent helical turns and disposed at nearly one side of helical cylinder. Despite an initial poly-Glu16 model has been built as standard α-helix structure, we have observed in local area of two these clusters the increased numbers of Cα-atoms per turn, to 5.0 and even 6.0 (Table 1). However, this occurs only in the area of excited atoms. Finally, we explain an existence of the clusters with shifted atoms. In helical structure every Cα-atom has four adjacent neighbors which are interacting in fluctuation traffic. The first interaction is connected with two adjacent atoms along the peptide chain, and it is determined by the potentials of internal rotations around bonds N-Cα and Cα-C. And the second interaction is due to the NH…O hydrogen bonds connecting the peptide groups at lower and higher helix turns.

4. Conclusion

The molecular dynamics of the helical poly-L-glutamic acid in water solution discloses *the distinctive fluctuation modes of*

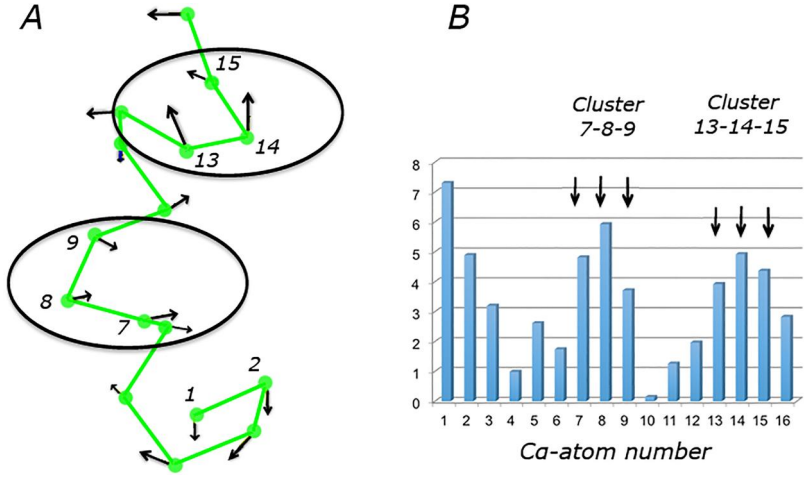

Figure 5. Example of most populated fluctuation mode observed for helical poly-L-glutamic acid, time frames 23–24 ns. *A* – Displacement of Cα-atoms, *B* – Cα-shifts, values are in Å. Two compared structures are marked with green and red colors. Clusters of excited atoms are encircled by ovals.

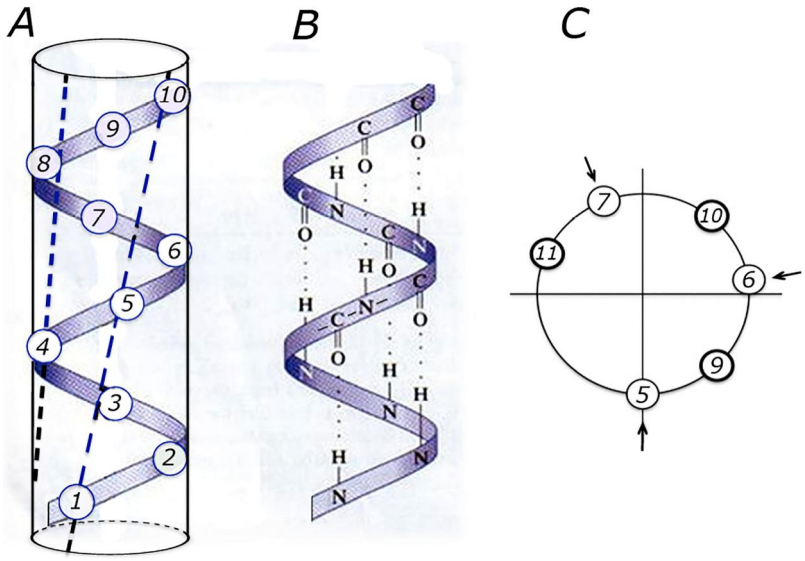

Figure 6. Structure of protein α-helix by Pauling and Corey (1951). *A*, Cα-atoms placed on the cylindrical surface; the dotted lines connect the closest residues of the adjacent turns bound by hydrogen bonds. *B*, Hydrogen bonds between peptide groups of the adjacent turns. *C*, α-Helix viewed along the helix axis, Cα-atoms of the first cluster 5–6–7 are indicated by arrows.

the helical structure. The modes include two clusters of fluctuation groups of Cα-atoms being localized in adjacent helical turns. The clusters of excited atoms are placed mainly on one side of the helix. The observed mode of fluctuation of polypeptide helix presents an intrinsic feature of this structure in solution. Therefore, these modes must be also displayed in the helix inside of globular protein. In fact, as a rule inside the protein molecule one side of helical fragment is bound with hydrophobic core, while another one is in water medium. This feature of helical PGA appears to determine the helix local stability and its dynamics. We suggest the further study of dynamics of globular proteins confirms that.

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Disclosure statement

The authors report there are no competing interests to declare.

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