

Title: Supplementary Movie 1: Sampling of Piezo1 by Yoda1 ligands.

Description: Multi-ligand trajectory (top view, 0 to 4.8 μ s, sampled every 24 ns) showing protein backbone in white surface, phosphate groups as dots and each Yoda1 ligand (Van der Waals representation) in a unique color.

Title: Supplementary Movie 2: Activation of the R2135A mutant with Yoda1.

Description: Δ PZ1 cells co-expressing GCaMP6m and the R2135A mutant were imaged for one minute at 1 frame/sec under epifluorescence illumination. 100 μ M Yoda1 was added at $t = 10$ s. The images are displayed at 1 frame s^{-1} .

Title: Supplementary Movie 3: Stretch-induced Piezo1 motions, side view.

Description: Multi-ligand trajectory (side view, 0 to 6.9 μ s, sampled every 24 ns) showing protein backbone (new cartoon, silver), phosphate groups (yellow spheres) and the L13 ligand (blue, Van der Waals representation).

Title: Supplementary Movie 4: Stretch-induced Piezo1 motions, top view.

Description: Multi-ligand trajectory (top view, 0 to 6.9 μ s, sampled every 24 ns) showing protein backbone (new cartoon, silver), phosphate groups (yellow spheres) and the L13 ligand (blue, Van der Waals representation).

Title: Supplementary Movie 5: Tilt motion of Piezo1 arms.

Description: Projection of the top 3 principal component modes clustered using the HDBSCAN method. The centers of each cluster were then computed and exported in pdb format for visualization.