Supplementary Methods

The TEMPO Integrator: Accelerating Molecular Simulations by Temporally-Multiscale Force Prediction

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Models.

All models were implemented in the open-source *Integrative Modeling Platform* (IMP) software (http://integrativemodeling.org) (Russel et al. 2012; Sali 2021; Michael P. Rout and Sali 2019).
Code and Data availability. https://github.com/ravehlab/tempo

5- and 10-bead models

Model components

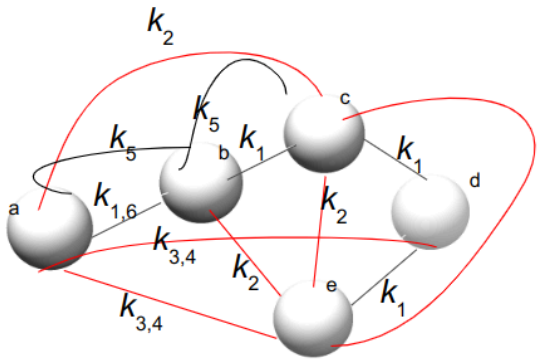

Figure S1. The 5-bead model. A visual representation of the 5-bead flexible polymer model of an intrinsically disordered protein, using a classic beads-on-a-string approach, augmented with non-bonded interactions. Each pair of consecutive beads (a–e) is bonded via a harmonic restraint (black), while nonbonded interactions are handled by a truncated harmonic potential (red). A single bead represents a link in the polymer chain (e.g., several consecutive residues) rather than a single atom. The force coefficients of the springs are labeled k_1 through k_n (Table 3). The notation ki,j is used to indicate that it encompasses both ki and kj

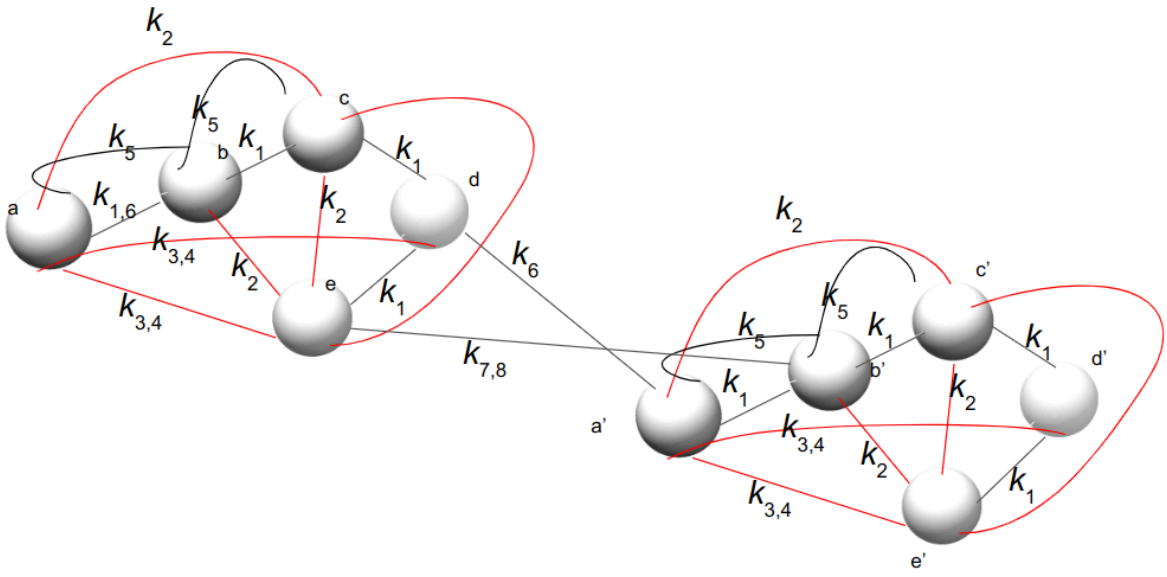

Figure S2. The 10-bead model. A visual representation of the 10-bead flexible polymer model of an intrinsically disordered protein, following a classic beads-on-a-string approach, augmented with non-bonded interactions. Consecutive beads are bonded via harmonic restraints (black), while nonbonded interactions are represented by truncated harmonic potentials (red). Each bead, labeled a–e and a′–e′, represents a coarse-grained link (e.g., several consecutive residues) rather than an individual atom. The force coefficients of the springs are labeled k_1 through k_n (Table 3). The notation ki,j is used to indicate that it encompasses both ki and kj e.g $k_{3,4}$ mean two forces are applied one with a spring constant of k_3 and the other with a spring constant of k_4

Polymer chains were represented using the beads on a string model. Each pair of beads was connected by a flexible spring. The beaded radii were uniformly set to 1 Å; we note that this relatively small size is an arbitrary choice that we used for benchmarking MSBD on the 5-bead and 10-bead toy systems (**Table 1)**, and it is not intended as a realistic physical representation. The interactions between consecutive beads were modeled using harmonic potentials with varying spring constants to capture heterogeneous interaction strengths typical of real-world systems (**Table 2-3)**.

Model interactions

The primary bonded interactions between consecutive beads in the chain were defined by the parameters of specific forces (**Table 3**, first row), ensuring the polymer's structural integrity. Additional local angular or bending interactions within the chain were modeled using the parameters in the fourth row, emphasizing flexibility. Long-range interactions between non-consecutive beads within the same chain were represented using parameters in the fifth and sixth rows, capturing reduced interaction strengths for distant bead pairs. Interactions reflecting steric constraints or specific long-range associations were

modeled using parameters from the last two rows, where stronger constraints were applied due to larger radii or specific structural properties.

The harmonic potentials for these interactions were implemented using IMP's HarmonicDistancePairScore and SphereDistancePairScore, with parameters specific to each interaction type, as described in the table. The simulation was conducted at room temperature (T=298.15K), and the spring constants were scaled based on thermal energy.

Component	Relevant IMP classes	Main parameters	Comments
simple polymer models	Particle, XYZR, Diffusion	Bead radius: 1 A Beads per chain (excluding anchor bead): 5-10 Diffusion coefficient: computed by Stokes' law	Each chain is represented as a flexible string of beads.

Table 1. Summary of the simple polymer model components, including technical representation in the Integrative Modeling Platform (IMP)(Russel et al. 2012).

Forces	Relevant IMP classes	Main parameters	Relevant particles
*U*specific	IMP.core.HarmonicDistancePairScore	center Spring constant k	All balls
*U*non-specific	IMP.core.SphereDistancePairScore(IMP.core.TruncatedHarmonicUpperBound	center, Spring constant k, threshold	All balls

Table 2. Summary of forces used in the polymer model, including technical representation in the Integrative Modeling Platform (IMP)(Russel et al. 2012).

Restraint name	IMP Restraint type	Parameters (center A, string, kcal/mol/A)	Restrained pairs of beads
k1	IMP.core.HarmonicDistancePairScore	(4, T_k*1.8)	a-b, b-c, c-d, d-e a-b, b'-c', c'-d', d'-e'
k2	IMP.core.SphereDistancePairScore	IMP.core.TruncatedHarmonicUpperBound(10., T_k, 11)	a-c, b-d, c-e a,-c,, b,-d,, c,-e,
k3	IMP.core.SphereDistancePairScore	IMP.core.TruncatedHarmonicUpperBound(8., T_k/16, 13)	a-e, a-d a'-e', a'-d'
k4	IMP.core.HarmonicDistancePairScore	(12, T_k/16)	a-e, a-d a'-e', a'-d'
k5	IMP.core.HarmonicDistancePairScore	(17, T_k/64)	a-b, b-c a'-b', b'-c'
k6	IMP.core.HarmonicDistancePairScore	(4, T_k*18)	a-b, e-a'
k7	IMP.core.HarmonicDistancePairScore	(12, T_k/16)	e-b', d-a'
k8	IMP.core.HarmonicDistancePairScore	(17, 1.T_k/64)	d-a'

Table 3. Restraint types and parameters for the 5-bead and 10-bead systems (Figure 2, S1, S2), including technical representation of these restraints in the Integrative Modeling Platform (IMP) (Russel et al. 2012). The term **T_k = 447.225** represents the magnitude of the force in arbitrary units, where "T_k" specifically denotes a standardized measure of force within this system. Using 447.225 as the magnitude reflects the calculated intensity based on the defined parameters or physical context. The label T_k conveys a compact, universally interpretable notation for the force magnitude within this arbitrary framework, ensuring consistency and ease of reference across related analyses or calculations.

The Nuclear Pore Complex (NPC) model

Model components.

The simulated components include the NPC, the nuclear envelope (NE), the flexible FG repeat domains of FG Nups, and passively diffusing macromolecules, all enclosed within a bounding box. The configuration of these components is fully specified by a configuration vector *X* that includes all time-variable parameters, i.e. the spatial coordinates of the FG repeats and the passively-diffusing molecules. The system components were coarse-grained similar to their representation in Timney et al. 2016 to increase the computational efficiency of the simulations while reproducing key system properties regarding passive diffusion kinetics {Timney, Raveh, JCB 2016}{Kim et al, Nature 2018}.

Component	Relevant IMP classes	Main parameters	Comments
Nuclear envelope (NE) + NPC scaffold	SlabWithCylindricalPore	NPC radius: 90	The slab representing the NE is centered at Z=0 and oriented parallel to the XY plane.
FG repeats	Particle, XYZR, Diffusion	Bead radius: 8 nm Beads per chain (excluding anchor bead): 8 Diffusion coefficient: computed by Stokes' law Number of FGs per layer: 8 Number of layers: 1	Each chain is represented as a flexible string of beads. An anchor bead was added as the last bead in each chain. Its center was fixed to the cylinder walls, in evenly spaced layers spanning the NE (from the cytoplasmic to nuclear end), and a radially symmetric pattern.
Passively-diffusing molecules	Particle, XYZR, Diffusion	Radius: 8-20 A	
Bounding Box	BoundingBox3D	Size: 130 x 130 x 130 A^3	

* We use a downsized version of the real NPC {Kim et al., Nature 2018}, similar to the one used in Timney et al. 2016, which was nonetheless shown to reproduce key system properties regarding passive diffusion(Timney et al. 2016; Raveh et al. 2024).

Table 4 Summary of the simple NPC model components including technical representation in the Integrative Modeling Platform (IMP)(Russel et al. 2012).

Model interactions.

Forces	Relevant IMP classes	Main parameters	Comments	Relevant particles
Uexcluded	IMP.core.ExcludedVolumeRestraint	A list of all particles K excluded Slack (that effects speed) name		diffusers and FG
*U*FG-bond	IMP.core.HarmonicDistancePairScore	center Spring constant k		All FG balls
*U*non-specific	IMP.core.SphereDistancePairScore(IMP.core.TruncatedHarmonicLowerBound	center, Spring constant k, threshold		diffusers and FGs
*U*excluded Nuclear envelope (NE)	IMP.npctransport.SlabWithCylindricalPore.setup_particle IMP.npctransport.SlabWithCylindricalPorePairScore IMP.core.PairRe	p_slab, slab_height, slab_pore_radius force constant k		ɔdifusseres

	straint			
U excluded-bounding-box	IMP.core.BoundingBox3DSingletonScore IMP.core.HarmonicUpperBound IMP.container.SingletonsRestraint	IMP.algebra.BoundingBox3D distance, K_BB bb_harmonic, bb	IMP.algebra.Vector3D IMP.algebra.Vector3D	all

Table 5. Summary of interactions used in the NPC model including technical representation in the Integrative Modeling Platform (IMP)(Russel et al. 2012).

Component	Description/Class Used	Constants/Parameters	Values Extracted
Diffusers and FG	IMP.core.ExcludedVolumeRestraint	k_excluded, slack	k_excluded=1, slack=1
Beads of FG repeats	IMP.core.HarmonicDistancePairScore	center, Spring constant (k)	center=distance_between_particles, k=2
UFG-bond	IMP.core.HarmonicDistancePairScore	center, Spring constant (k)	center=16*1.9, k=2
Diffusers and FG	IMP.npctransport.SlabWithCylindricalPore	slab_height, slab_pore_radius, k_slab	slab_height=55, slab_pore_radius=90, k_slab=5
Uexcluded-bounding-box	IMP.core.BoundingBox3DSingletonScore	The bounding box (bb), distance, K_BB	bb=IMP.algebra.BoundingBox3D, K_BB=2
All	IMP.core.SphereDistancePairScore	center, Spring constant (k), threshold	center=3, k=0.002, threshold=5

Table 6. Restraint parameters for the NPC model. including technical representation of these restraints in the Integrative Modeling Platform (IMP) (Russel et al. 2012).

Equilibration

All the diffusing molecules were initialized randomly at the upper side of the NPC.
The model was then equilibrated for 1 microsecond with a step size of 2,000 fs at room temperature.