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Disorder-Induced Localization in Spliceosomal Conformational Networks for Resolving Plasmodium RNA–Driven Structural Perturbations and Predicting Functional Arrest

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ABSTRACT

The spliceosome is a highly dynamic protein-directed metalloribozyme that maintains eukaryotic gene expression through a precisely choreographed sequence of conformational rearrangements. While native splicing relies on the seamless exploration of a vast conformational landscape, recent evidence indicates that *Plasmodium falciparum* can deliver parasite-derived RNA into host nuclei to disrupt this machinery. However, a rigorous physical mechanism explaining how these localized perturbations trigger global functional arrest has remained elusive. Here, we develop a biophysical framework that demonstrates that spliceosomal dysfunction is driven by a disorder-induced localization transition within the complex's conformational state space. We apply a similarity transformation of the stochastic master equation to map the spliceosome's kinetic dynamics onto a Hermitian tight-binding Hamiltonian, where parasite-induced energetic perturbations appear as diagonal and off-diagonal disorder. Spectral analysis reveals the emergence of a critical disorder threshold, $\Lambda_{\text{crit}} = \sigma_{\epsilon}/\bar{t} \sim 1$, marking a transition from a delocalized regime characterized by extended conformational states and efficient sampling to a localized regime defined by confinement and kinetic trapping. Above this threshold, the effective conformational space collapses, leading to a sharp, nonlinear suppression of catalytic accessibility. We derive a scaling law for splicing efficiency, $\eta \sim \exp(-\alpha\Lambda^2)$, which quantitatively captures the onset of functional failure. This work shifts the paradigm of molecular pathology from simple biochemical inhibition to a global physical transition governed by Anderson-type localization. These results establish a direct relationship between molecular disorder and biological output, reframing spliceosomal pathology as a disorder-driven phase transition. Beyond its implications for malaria, this framework provides a universal diagnostic toolkit including localization length and inverse participation ratio to assess the resilience of macromolecular machines.

Keywords: Spliceosome dynamics, *Plasmodium falciparum* RNA interference, Anderson localization in biomolecular systems, Disorder-induced functional arrest, Conformational state networks

1.0. INTRODUCTION

The spliceosome, a colossal and highly dynamic protein-directed metalloribozyme, serves as the central gatekeeper of eukaryotic gene expression by executing the precise excision of introns from pre-messenger RNA[1-2]. This complex catalytic cycle is not a static assembly but a choreographed sequence of large-scale structural rearrangements that enable accurate transcript processing and proteomic diversity [3-4]. The spliceosome is further understood as a dynamic conformational system, where catalytic fidelity emerges from coordinated transitions across multiple intermediate states interconnected through stochastic and reversible pathways[5-6]. However, this finely tuned system is vulnerable to molecular

perturbations. Recent evidence demonstrates that *Plasmodium falciparum*, the causative agent of malaria, can deliver parasite-derived RNA into host cell nuclei, where it directly rewires host splicing machinery [7-9]. This finding reinforces a broader understanding that disruption of this precisely orchestrated process is a key driver of human diseases, including cancer, neurodegeneration, and immune dysfunction[10-11]. This raises a fundamental question: how do localized parasite-induced perturbations disrupt the globally coordinated dynamics of the spliceosome?

This question remains largely unresolved in the current literature, primarily due to the reliance on structural, biochemical, and computational approaches that model spliceosomal dynamics as a system governed by isolated molecular interactions rather than as a high-dimensional, dynamically coupled conformational network. Specifically, several models interpret spliceosomal dysfunction in terms of static structural interference or disrupted molecular interactions, without accounting for the inherently high-dimensional, stochastic, and dynamically coupled nature of spliceosomal conformational transitions[4,12]. Cryo-electron microscopy has provided high-resolution snapshots of spliceosomal intermediates, revealing key catalytic configurations and structural transitions throughout the splicing cycle[13-14]. Complementary structural and biochemical studies have further elucidated the molecular determinants of catalytic activation and fidelity[15-16]. At the same time, single-molecule fluorescence techniques have uncovered the stochastic and reversible nature of spliceosomal transitions, highlighting the importance of dynamic coordination across multiple intermediate states[5,6,17-19]. Computational frameworks, including molecular dynamics simulations and Markov state models, have advanced the understanding of conformational energy landscapes and transition kinetics in biomolecular systems[20-22]. More recently, network-based analyses have conceptualized the spliceosome as an interconnected system of conformational states, where global functionality emerges from coordinated transitions across the network[23]. Despite these advances, existing applications of these approaches have largely focused on near-native or unperturbed conditions, and therefore do not explicitly address how exogenous perturbations such as parasite-derived RNA alter the global connectivity and accessibility of conformational states. As a result, while these studies have successfully characterized spliceosomal structure and dynamics under native conditions, they remain insufficient to explain how localized perturbations translate through the system to produce widespread functional arrest. These approaches have also failed to account for how exogenous agents, such as Plasmodium-derived RNA, introduce inhomogeneous energetic perturbations that effectively act as sources of structural and dynamical disorder within the spliceosomal conformational landscape. Therefore, the fundamental problem is to determine whether and how parasite RNA-induced disorder leads to localization of spliceosomal conformational dynamics, effectively trapping the system within a restricted subset of states and preventing progression along the functional splicing pathway.

This study proposes that Plasmodium RNA-induced structural perturbations introduce effective disorder into the spliceosomal conformational energy landscape, leading to localization of conformational state accessibility and restricting the system to a limited subset of accessible states. This localization disrupts the coordinated progression of structural transitions required for catalytic activity, thereby providing a physics-based mechanism for spliceosomal functional arrest under parasite RNA occupancy. To substantiate this hypothesis, we develop a theoretical framework that adapts the mathematical formalism of Anderson localization, originally formulated for quantum wavefunctions in disordered potentials[24-25], to characterize conformational state accessibility in a disordered biomolecular energy landscape[26]. This approach leverages a formal mathematical correspondence between tight-binding

Hamiltonians and rate matrices governing conformational transitions[27], enabling the mapping of stochastic state dynamics onto an effective spectral representation in the limit where intra-state thermal fluctuations are fast relative to inter-state conformational transitions. Within this framework, parasite RNA-induced perturbations are treated as spatially inhomogeneous and effectively quenched sources of energetic disorder, which modify the connectivity and accessibility of conformational states[28]. The scope of this work encompasses a multiscale description of spliceosomal dynamics, linking localized perturbations to global alterations in conformational state accessibility. By shifting the paradigm from static structural inhibition to disorder-induced dynamical arrest, this study provides a unifying, physics-informed framework for understanding spliceosomal dysfunction. More generally, it provides a conceptual foundation for the development of therapeutic strategies aimed at restoring catalytic fluidity in host cellular machinery of biomolecular systems compromised by pathogenic perturbations.

2.0. METHODS

2.1. Biophysical Description of the Spliceosome Conformational Network

The spliceosome operates as a conformational network with a high-dimensional landscape of interconnected structural states through which the machine traverses to accomplish catalytic activation and intron excision. Each conformational state corresponds to a distinct arrangement of the RNA–protein catalytic core, defined by measurable structural parameters such as the inter-metal distance between catalytic Mg^{2+} ions ($\sim 3.8 - 4.2 \text{ \AA}$), positioning of the branch point adenosine, and coordination geometry of the U6 snRNA catalytic triplex[2,29]. Transitions between these states are inherently stochastic, governed by thermal fluctuations that enable the system to explore multiple pathways prior to catalytic commitment [5,6]. This stochasticity underpins spliceosomal proofreading, allowing rejection of misassembled intermediates and ensuring catalytic fidelity[30].

Spliceosomal dynamics span multiple temporal and spatial scales. Local fluctuations in RNA backbone geometry and metal coordination occur on picosecond to nanosecond timescales, whereas large-scale conformational rearrangements, such as U4/U6 unwinding, Prp2-mediated remodeling, and activation transitions occur on millisecond to second timescales[22,31]. These processes occur over length scales ranging from sub-ångström bond distortions ($\sim 0.5\text{--}1.0 \text{ \AA}$) to nanometer-scale domain motions ($\sim 1\text{--}10 \text{ nm}$). The underlying energy landscape is rugged, consisting of metastable basins separated by barriers typically on the order of $5\text{--}15 \text{ kcal/mol}$, comparable to the magnitude of thermal fluctuations ($kT \approx 0.6 \text{ kcal/mol}$ at physiological temperature) and RNA–protein interaction energies[20,26]. This ruggedness reflects residual local frustration, regions where interactions are suboptimal, creating multiple metastable substates and alternative pathways even under native conditions[32–35]. This means that even modest perturbations to the energy landscape have disproportionately large dynamical consequences: a perturbation of just $2\text{--}5 \text{ kcal/mol}$ (well within the energetic scale of RNA binding), readily induced by the binding of an exogenous RNA can result in a $\sim 30\text{--}4,000$ -fold reduction in transition rates, effectively freezing the system's progression through the conformational network. Thus, spliceosomal function depends not on a single deterministic pathway but on the accessibility and connectivity of multiple conformational states across this landscape.

The spliceosome operates within a crowded nuclear environment where electrostatic interactions and ionic conditions play a dominant role. The effective dielectric constant within the spliceosomal core is reduced relative to bulk solvent ($\epsilon \approx 2\text{--}10$), enhancing electrostatic coupling between RNA phosphates, protein residues, and catalytic ions[36]. Monovalent (K^+) and divalent (Mg^{2+}) ions actively stabilize tertiary structure and catalytic geometry. The catalytic Mg^{2+} ions generate local electric fields on the order of 10^9

V/m, which polarize the scissile phosphate and lower activation barriers for transesterification [2]. Perturbations as small as 1–2 Å in ion positioning or ~0.5 Å in bond geometry can shift activation energies by 2–5 kcal/mol, sufficient to disrupt catalysis given the narrow energetic margins governing spliceosomal transitions.

Perturbation by malaria parasite (*Plasmodium falciparum*)-derived RNA introduces localized energetic heterogeneity through binding interactions with spliceosomal proteins such as ACIN1 and PNN[7,37]. These interactions modify hydrogen bonding networks, impose steric constraints, and alter local electrostatic environments, resulting in perturbations on the order of 3–15 kcal/mol when combining binding energies and conformational penalties[38–39]. Because these perturbations are spatially localized, they introduce inhomogeneous disorder across the conformational landscape, selectively altering the stability of specific states and the accessibility of transition pathways. As a result, the effective connectivity of the conformational network is reduced, and the system becomes increasingly biased toward kinetically trapped, non-productive states. The multiscale nature of spliceosomal dynamics and their sensitivity to energetic perturbations are summarized schematically in Figure 1, which illustrates how parasite RNA binding translates into structural, energetic, and dynamical disruption.

Figure 1. Parasite RNA–Induced Biophysical Perturbation of Spliceosomal Conformational Dynamics

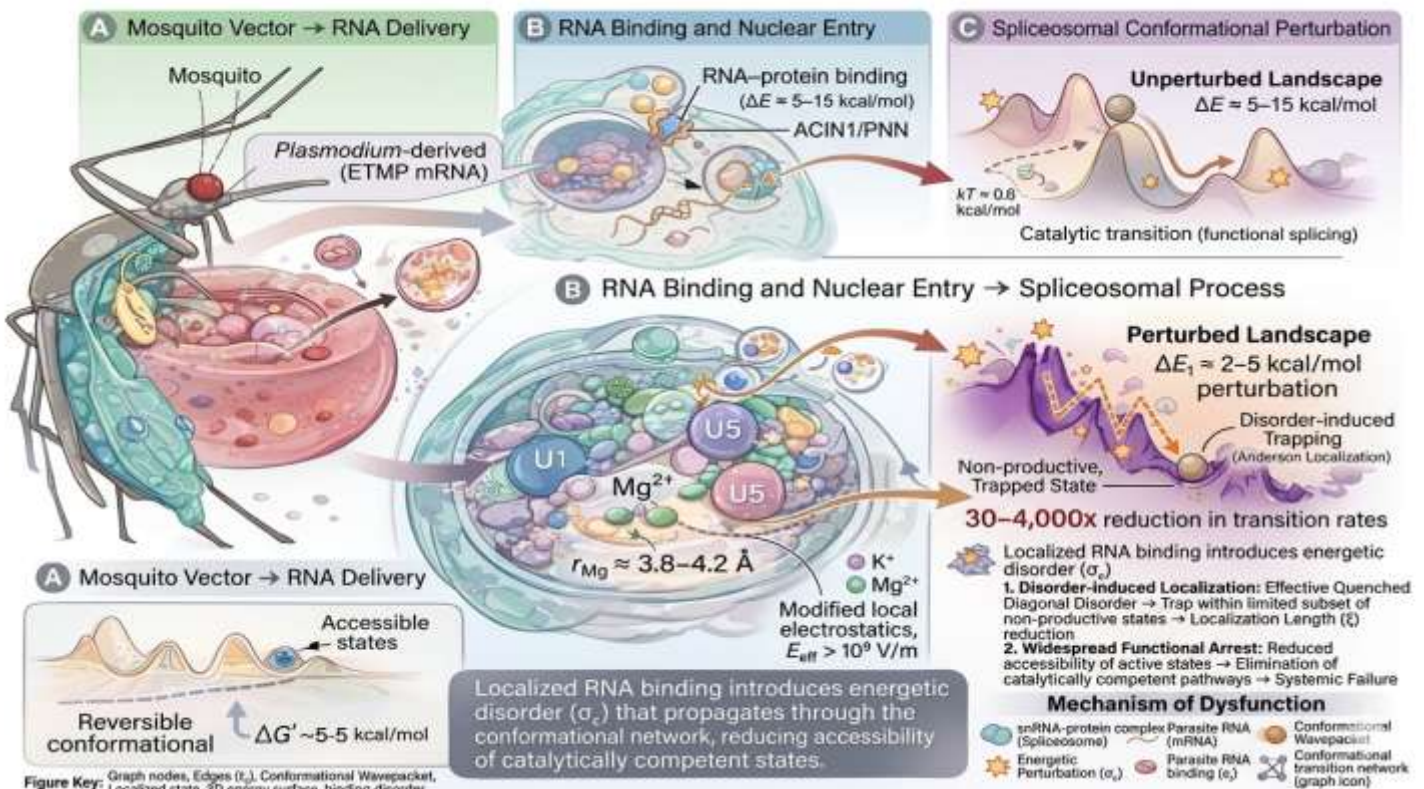


Figure 1. Parasite RNA–Induced Biophysical Perturbation of Spliceosomal Conformational Dynamics.

(A) Transmission of *Plasmodium falciparum*-derived RNA via the mosquito vector and subsequent delivery into host cells through extracellular vesicles. (B) Nuclear uptake of parasite RNA and binding to spliceosomal regulatory proteins (e.g., ACIN1 and PNN), introducing interaction energies on the order of 5–15 kcal/mol. (C) Biophysical consequences of RNA binding on spliceosomal conformational dynamics. In the unperturbed state, the spliceosome traverses a smooth energy landscape with barriers of ~5–15 kcal/mol, enabling reversible transitions and catalytic progression. In the perturbed state, localized energetic shifts of ~2–5 kcal/mol alter catalytic Mg^{2+} positioning ($r_{Mg} \approx 3.8\text{--}4.2$ Å) and electrostatic fields ($E_{eff} \sim 10^9$ V/m), leading to rugged energy landscapes, suppressed transition rates (30–4,000-fold reduction), and trapping in non-productive states.

This figure establishes the physical basis for parasite-induced energetic disorder and its propagation through the spliceosomal conformational network.

To capture these dynamics quantitatively, we model the spliceosomal conformational landscape as a graph $G = (V, E)$, where each vertex $v_i \in V$ represents a distinct conformational state defined by collective coordinates derived from molecular dynamics simulations or cryo-EM ensembles, and each edge $e_{ij} \in E$ represents a possible transition between states with an associated effective coupling t_{ij} derived from the corresponding transition rates. The energetic cost of occupying a given conformational state is encoded as an on-site energy ϵ_i . The resulting tight-binding-type operator

$$H = \sum_i \epsilon_i |i\rangle\langle i| + \sum_{\langle i,j \rangle} t_{ij} (|i\rangle\langle j| + |j\rangle\langle i|)$$

admits a spectral decomposition obtained by solving the associated time-independent Schrödinger-like eigenvalue problem

$$H\psi_\alpha = E_\alpha\psi_\alpha,$$

which is mathematically equivalent to the diagonalization of the symmetrized rate operator. The eigenstates ψ_α characterize the accessibility structure of the conformational network, while the eigenvalues E_α define the hierarchy of relaxation modes.

For the low effective spectral dimension of protein conformational networks ($d_s \approx 1.5\text{--}1.8$), the scaling theory of Anderson localization predicts that eigenstates become spatially localized when the disorder strength $\sigma_\epsilon/\bar{t}$ exceeds a critical threshold. In this regime, localization restricts access to distant conformational states and suppresses global exploration of the energy landscape.

The dynamical consequences of this localization are described through the spectral evolution of probability amplitudes derived from the eigenbasis. At long timescales relevant to spliceosomal function, the dynamics are governed by classical stochastic transitions between localized states, with transition rates determined by thermally activated barrier crossing processes consistent with transition state theory. This combined spectral–stochastic framework, based on the solution of a Schrödinger-like eigenvalue problem for the symmetrized rate operator, provides an analytically tractable description of conformational dynamics grounded in realistic biophysical parameters while capturing the essential physics of disorder-induced dynamical arrest.

Figure 2 presents a reduced representation of spliceosomal dynamics in terms of energy landscapes, network connectivity, and state accessibility under varying disorder regimes.

Figure 2. Disorder-Induced Localization and Trapping in the Spliceosomal Conformational Network

A physics-informed model illustrating how exogenous RNA binding creates energetic disorder, fragments the network, and traps conformational dynamics, leading to functional arrest.

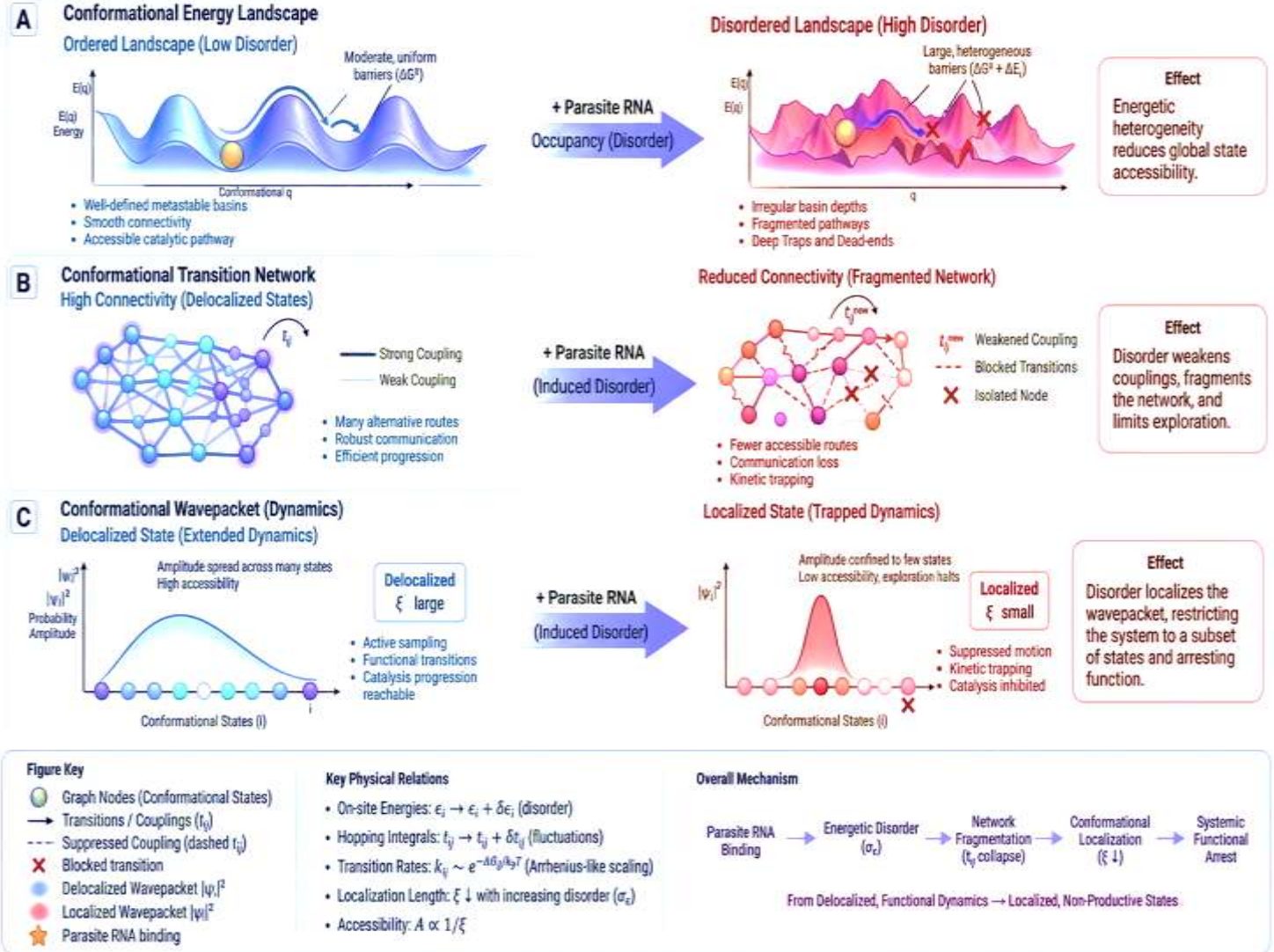


Figure 2. Disorder-Induced Localization in the Spliceosomal Conformational Network.

(A) Conformational energy landscapes represented along an effective reaction coordinate q . In the low-disorder regime, the landscape exhibits well-defined metastable basins and uniform barrier heights, supporting accessible catalytic pathways. In the high-disorder regime, parasite RNA occupancy introduces energetic heterogeneity ($\Delta E_i \sim 3\text{--}15$ kcal/mol), resulting in irregular basin depths, fragmented pathways, and deep trapping regions. (B) Network representation of spliceosomal conformational states. Under low disorder, the network is highly connected with strong inter-state couplings (t_{ij}), enabling efficient exploration. Under high disorder, couplings are weakened or suppressed, leading to fragmentation, reduced connectivity, and isolated nodes corresponding to kinetically trapped states. (C) Conformational wavepacket representation of system dynamics. In the ordered regime, the probability amplitude is delocalized across many states, reflecting high accessibility and functional dynamics. In the disordered regime, the amplitude becomes localized over a limited subset of states, corresponding to reduced accessibility and kinetic trapping. This figure provides a physics-informed interpretation of spliceosomal dysfunction as a disorder-induced localization phenomenon.

For modelling purposes, each spliceosomal conformational substate is characterized by a small set of physically interpretable parameters: the catalytic Mg^{2+} separation r_{Mg} , the branch-site and catalytic-core

coordinates (q_b, q_c) , the state energy E_i , the inter-state barrier $\Delta G_{ij}^\ddagger$, and the transition rate k_{ij} . Parasite RNA binding is described through an interaction energy E_{bind} , an induced conformational penalty E_{pen} , and an effective disorder amplitude σ_E that captures the resulting heterogeneity across the conformational landscape. Values for these parameters are drawn from literature and summarized in Table 1.

Table 1. Core Biophysical Parameters for Spliceosomal Dynamics and Perturbation

Symbol	Value / Range	Units	Role	Source
$r_{\text{Mg-Mg}}$	3.8–4.2	Å	Catalytic Mg^{2+} separation defining active-site geometry	[2,29]
E_{loc}	$\sim 10^9$	V m ⁻¹	Local electric field at catalytic center	[2, 36]
τ_{fast}	ps–ns	s	Local backbone and ion-coordination fluctuations	[22, 39]
τ_{slow}	ms–s	s	Global conformational transitions (activation, remodeling)	[5, 31]
k_{hel}	1–10	s ⁻¹	Helicase-driven remodeling rate	[31,41]
$\Delta G^\ddagger$	5–15	kcal mol ⁻¹	Energy barrier between metastable conformations	[20,26]
$k_B T(310\text{ K})$	≈ 0.6	kcal mol ⁻¹	Thermal energy scale	Standard thermodynamic relation
ϵ_{eff}	2–10	—	Effective dielectric constant of spliceosomal core	[26,36]
$E_{\text{bind}}^{\text{RNA-protein}}$	5–15	kcal mol ⁻¹	RNA–protein / RNA–RNA binding energy scale	[38, 39]
E_{pen}	3–8	kcal mol ⁻¹	Conformational accommodation penalty	[26,39]

Parameter ranges are compiled from structural, single-molecule, and computational studies of spliceosomal dynamics and RNA–protein interactions. These values define the energetic and kinetic scales used to parameterize the reduced conformational landscape in this study.

The correspondence between the biophysical system and a disorder-driven localization framework is explicitly mapped in Figure 3, which provides the conceptual foundation for the theoretical formulation developed in the subsequent section.

Mapping *Plasmodium* RNA Sabotage onto the Conformational State Space

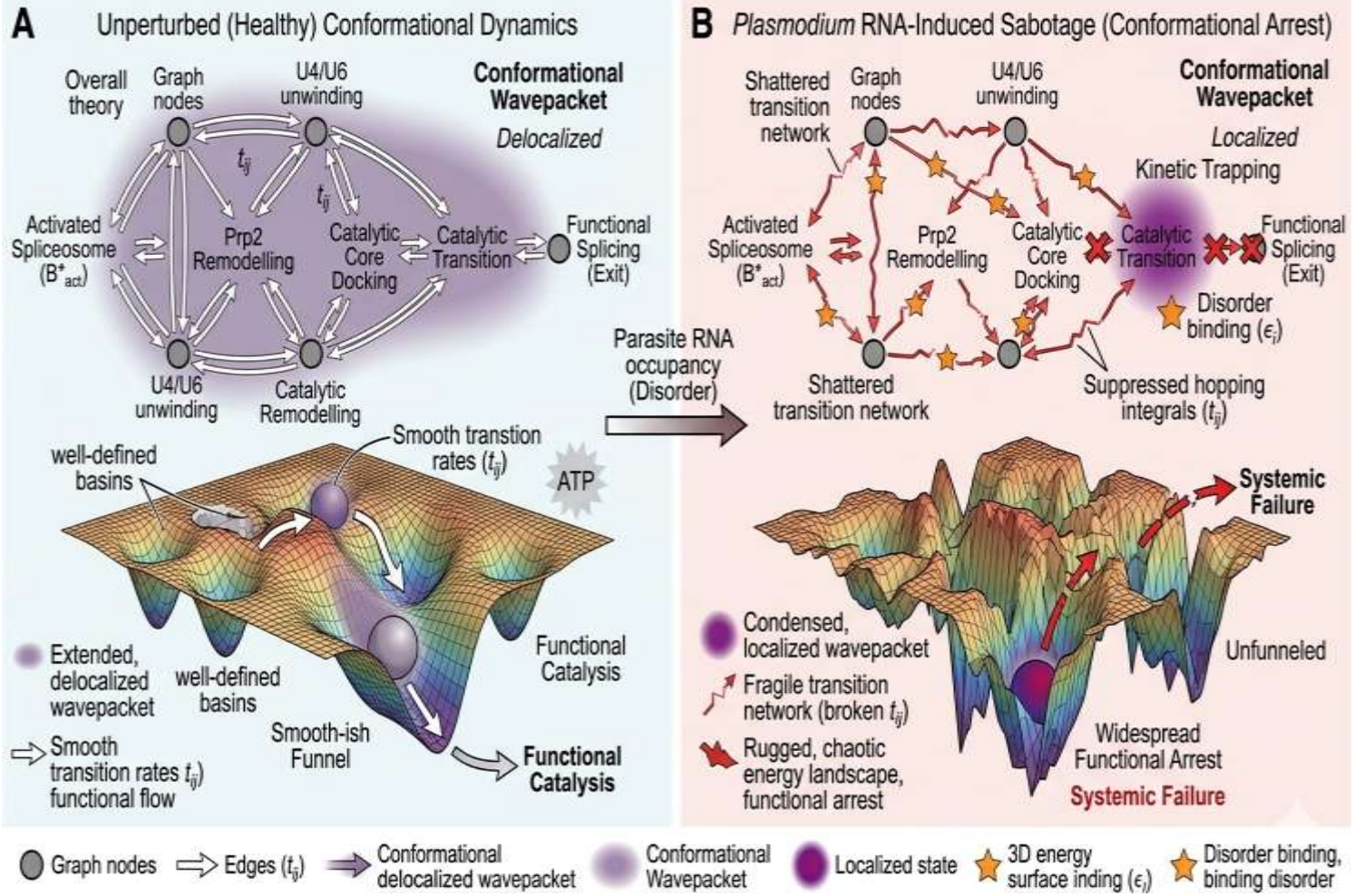


Figure 3. Mapping *Plasmodium* RNA-Induced Perturbation onto Conformational State Space.

(A) In the unperturbed state, spliceosomal conformational dynamics are represented as a well-connected network with smooth transition rates (t_{ij}), supporting a delocalized conformational wavepacket that spans multiple functional states. The associated energy landscape exhibits well-defined basins and a funnel-like topology, enabling efficient catalytic progression. (B) Upon parasite RNA binding, the conformational network becomes fragmented due to the introduction of disorder in state energies (ϵ_i) and suppression of inter-state couplings (t_{ij}). This results in a rugged, chaotic energy landscape with irregular barriers and deep trapping regions. The conformational wavepacket becomes localized, restricting dynamics to a limited subset of non-productive states and preventing access to catalytically competent configurations.

This mapping establishes the correspondence between spliceosomal conformational dynamics and Anderson-type localization, where disorder-induced suppression of state accessibility leads to kinetic trapping and functional arrest.

2.2. Analytical Formulation of the Disordered Spliceosomal Effective Potential

The spliceosomal system evolves on a high-dimensional conformational landscape governed by collective structural coordinates associated with catalytic activation and intron excision. Let the full molecular configuration be described by generalized coordinates $\mathbf{R}$, with Hamiltonian

$$\hat{H} = - \sum_{\alpha} \frac{\hbar^2}{2m_{\alpha}} \nabla_{\alpha}^2 + U(\mathbf{R}) \quad (1)$$

where the sum runs over all atomic degrees of freedom. To obtain a tractable representation consistent with the separation of timescales ($\tau_{\text{fast}} \ll \tau_{\text{slow}}$), the coordinates are partitioned as $\mathbf{R} = (\mathbf{Q}, \mathbf{X})$, where $\mathbf{Q}$ denotes slow collective conformational modes and $\mathbf{X}$ denotes fast local degrees of freedom. Adiabatic elimination of $\mathbf{X}$ yields the potential of mean force:

$$V_{\text{eff}}(\mathbf{Q}) = -k_B T \ln \left[\int d\mathbf{X} e^{-\beta U(\mathbf{Q}, \mathbf{X})} \right] \quad (2)$$

Where $\beta = (k_B T)^{-1}$

Since spliceosomal progression occurs through a finite set of metastable conformational states (e.g., B, B^{act} , B^* , C, P, etc.), the multidimensional coordinate $\mathbf{Q}$ is projected onto a reduced collective coordinate q that captures dominant structural rearrangements associated with catalytic competence. The reduced coordinate q is taken as the root-mean-square deviation (RMSD) of the catalytic core relative to a reference structure, or the first principal component from molecular dynamics simulations of spliceosomal transitions[14,15]. The effective Hamiltonian is therefore:

$$\hat{H}_{\text{eff}} = -\frac{\hbar^2}{2\mu} \frac{d^2}{dq^2} + V_{\text{eff}}(q) \quad (3)$$

where μ is the effective mass associated with the slow conformational motion on the reduced collective coordinate q . It is obtained by projecting the full atomic kinetic energy onto the conformational path $\mathbf{R}(q)$, so that

$$\frac{1}{2} \sum_{\alpha} m_{\alpha} |\dot{\mathbf{r}}_{\alpha}|^2 = \frac{1}{2} \mu(q) \dot{q}^2, \mu(q) = \sum_{\alpha} m_{\alpha} \left| \frac{\partial \mathbf{r}_{\alpha}}{\partial q} \right|^2 \quad (4)$$

For analytical tractability, $\mu(q)$ is approximated by a constant basin-averaged value μ_0 , evaluated from the dominant conformational mode extracted from structural ensembles or molecular dynamics trajectories. This follows directly from the transformation of the kinetic energy under generalized coordinates and is standard in the treatment of collective variables and reduced-dimensional molecular dynamics[20,40-41].

The functional form of $V_{\text{eff}}(q)$ must reflect the experimentally established features of the spliceosomal landscape: finite metastable basins, asymmetric escape behavior, and barrier heights on the order of $\Delta G^{\ddagger} \sim 5\text{--}15$ kcal/mol[20,22]. According to the principle of minimal frustration[32], evolved biomolecular systems are funneled toward functional states, meaning that the energy landscape is predominantly smooth with a bias toward the catalytically active conformation. However, residual local frustration persists, regions where interactions are suboptimal, creating multiple metastable substates and alternative pathways even under native conditions[33,35].

Each metastable conformational state is therefore represented by an analytically solvable Morse potential, which captures finite binding, anharmonicity, and asymmetric escape:

$$V_i^{(0)}(q) = D_i^{(0)} \left[e^{-2a_i^{(0)}(q-q_i^{(0)})} - 2e^{-a_i^{(0)}(q-q_i^{(0)})} \right] \quad (5)$$

where $D_i^{(0)}$ is the basin depth, $a_i^{(0)}$ defines the inverse width (stiffness), and $q_i^{(0)}$ specifies the equilibrium configuration of the i -th state in the unperturbed (native) landscape. For spliceosomal states, typical Morse parameters are: $D_i^{(0)} \approx 5\text{--}15$ kcal/mol, $(a_i^{(0)})^{-1} \approx 0.5\text{--}2$ Å, and state separation $q_{i+1}^{(0)} - q_i^{(0)} \approx 3\text{--}7$ Å[14,16,39].

To incorporate frustration as intrinsic disorder we quantify Local frustration by the variance in the energetic landscape even in the absence of exogenous perturbations. Following the frustratometer formalism [33,42], we model frustration as small, correlated random shifts to the Morse parameters:

$$D_i^{(0)} \rightarrow D_i^{(0)} + \delta D_i^{(\text{frust})}, a_i^{(0)} \rightarrow a_i^{(0)} + \delta a_i^{(\text{frust})}, q_i^{(0)} \rightarrow q_i^{(0)} + \delta q_i^{(\text{frust})} \quad (6)$$

where $\delta D_i^{(\text{frust})}$, $\delta a_i^{(\text{frust})}$, and $\delta q_i^{(\text{frust})}$ are drawn from distributions with zero mean and variances $\sigma_{D,\text{frust}}^2$, $\sigma_{a,\text{frust}}^2$, and $\sigma_{q,\text{frust}}^2$. From experimental and computational estimates of frustration magnitudes in RNA-protein complexes[35], the characteristic energetic variance due to frustration is $\sigma_{\epsilon,\text{frust}} \approx 0.5\text{--}1.0$ kcal/mol. This intrinsic disorder ensures that even the native spliceosomal landscape is not perfectly smooth but contains residual ruggedness that influences conformational dynamics.

The binding of *Plasmodium*-derived ETMP mRNA to peripheral spliceosomal proteins ACIN1 and PNN[7] introduces additional, larger-magnitude structural perturbations. Because the RNA binds stably on the timescale of individual splicing transitions (μs – ms), the disorder is treated as quenched, static on the timescale of conformational dynamics. These perturbations are incorporated as additional random shifts to the Morse parameters:

$$D_i = D_i^{(0)} + \delta D_i^{(\text{frust})} + \delta D_i^{(\text{para})}, a_i = a_i^{(0)} + \delta a_i^{(\text{frust})} + \delta a_i^{(\text{para})}, q_i = q_i^{(0)} + \delta q_i^{(\text{frust})} + \delta q_i^{(\text{para})} \quad (7)$$

where $\delta D_i^{(\text{para})}$, $\delta a_i^{(\text{para})}$, and $\delta q_i^{(\text{para})}$ are drawn from distributions with variances determined by RNA binding energies (5–15 kcal/mol) and conformational penalties (3–8 kcal/mol) [38,39].

The total on-site energy variance is therefore:

$$\sigma_\epsilon^2 = \sigma_{\epsilon,\text{frust}}^2 + \sigma_{\epsilon,\text{para}}^2 \quad (8)$$

with $\sigma_{\epsilon,\text{para}} \approx 2\text{--}5$ kcal/mol, giving a combined $\sigma_\epsilon \approx 2.1\text{--}5.1$ kcal/mol.

Combining the native Morse potentials with frustration and parasite-induced perturbations, the total potential for each basin is:

$$V_i(q) = \left(D_i^{(0)} + \delta D_i^{(\text{frust})} + \delta D_i^{(\text{para})} \right) \zeta \quad (9a)$$

Where

$$\zeta = \left[e^{-2(a_i^{(0)} + \delta a_i^{(\text{frust})} + \delta a_i^{(\text{para})})(q - q_i^{(0)} - \delta q_i^{(\text{frust})} - \delta q_i^{(\text{para})})} - 2e^{-(a_i^{(0)} + \delta a_i^{(\text{frust})} + \delta a_i^{(\text{para})})(q - q_i^{(0)} - \delta q_i^{(\text{frust})} - \delta q_i^{(\text{para})})} \right]$$

Expanding to first order in perturbations:

$$\delta V_i(q) = \frac{\partial V_i}{\partial D_i} \delta D_i + \frac{\partial V_i}{\partial a_i} \delta a_i + \frac{\partial V_i}{\partial q_i} \delta q_i + O(\delta^2) \quad (9b)$$

with:

$$\begin{aligned} \frac{\partial V_i}{\partial D_i} &= e^{-2a_i(q - q_i)} - 2e^{-a_i(q - q_i)}, \frac{\partial V_i}{\partial a_i} = D_i [-2(q - q_i)e^{-2a_i(q - q_i)} + 2(q - q_i)e^{-a_i(q - q_i)}] \text{ and } \frac{\partial V_i}{\partial q_i} \\ &= 2a_i D_i [e^{-2a_i(q - q_i)} - e^{-a_i(q - q_i)}] \end{aligned}$$

The global conformational landscape is constructed as a superposition of such metastable basins:

$$V_{\text{eff}}(q) = \sum_{i=1}^{N_s} \chi_i(q) V_i(q) \quad (10)$$

where N_s is the number of distinct metastable conformational states in the spliceosomal cycle, and $\chi_i(q)$ are smooth partition functions satisfying $\sum_i \chi_i(q) = 1$.

A convenient choice is:

$$\chi_i(q) = \frac{\exp\left(-\frac{(q-q_i)^2}{2\sigma^2}\right)}{\sum_{j=1}^{N_s} \exp\left(-\frac{(q-q_j)^2}{2\sigma^2}\right)} \quad (11)$$

where σ sets the width of the transition region between states.

The Morse potential is chosen as the minimal analytically solvable form capturing finite binding, anharmonicity, and asymmetric barrier crossing observed in biomolecular transitions.

Mapping to the Anderson Tight-Binding Hamiltonian

The continuous potential $V_{\text{eff}}(q)$ is discretized onto the conformational graph $\mathcal{G} = (V, E)$ by identifying each local minimum q_i as a vertex $|i\rangle$ and computing the on-site energy $\epsilon_i = V_{\text{eff}}(q_i)$. The hopping integrals t_{ij} between neighbouring states are obtained from the barrier heights via:

$$t_{ij} \approx \hbar\omega_0 e^{-\Delta G_{ij}^\ddagger/2k_B T} \quad (12)$$

where $\Delta G_{ij}^\ddagger$ is the barrier height between states i and j , extracted from the Morse potential parameters.

The resulting tight-binding Hamiltonian is:

$$\hat{H}_{\text{TB}} = \sum_i \epsilon_i |i\rangle\langle i| + \sum_{\langle i,j \rangle} t_{ij} (|i\rangle\langle j| + |j\rangle\langle i|) \quad (13)$$

where the on-site energies contain both intrinsic frustration and parasite-induced disorder:

$$\epsilon_i = \epsilon_i^{(0)} + \delta\epsilon_i^{(\text{frust})} + \delta\epsilon_i^{(\text{para})} \quad (14)$$

The total disorder strength is:

$$\frac{\sigma_\epsilon}{\bar{\epsilon}} = \frac{\sqrt{\sigma_{\epsilon,\text{frust}}^2 + \sigma_{\epsilon,\text{para}}^2}}{\bar{\epsilon}} \quad (15)$$

The prefactor $\hbar\omega_0$ in Eq.(12) arises from the quantum mechanical treatment of transition amplitudes in the tight-binding representation and plays the role of an attempt frequency for conformational transitions. For the relevant vibrational modes of the spliceosomal core, characteristic frequencies are typically in the range $\omega_0 \sim 10^{12}\text{--}10^{13} \text{ s}^{-1}$, corresponding to bond vibrations and local RNA fluctuations[43-44]. This yields an energy scale $\hbar\omega_0 \sim 0.1\text{--}1 \text{ kcal/mol}$, which is comparable to the thermal energy $k_B T \approx 0.6 \text{ kcal/mol}$ at physiological temperature. In the high-temperature limit, the quantum prefactor reduces to the classical Kramers rate prefactor $\nu \approx \omega_0/2\pi$, consistent with transition state theory for activated processes in condensed-phase systems[45-46]. More generally, dissipative quantum treatments of barrier crossing recover this correspondence between quantum and classical prefactors in the appropriate limit[47]. The use of $\hbar\omega_0$ therefore provides a consistent bridge between quantum mechanical and semiclassical descriptions of conformational transitions. For biomolecular systems, both experimental measurements and molecular simulations report attempt frequencies in the range $10^{12}\text{--}10^{13} \text{ s}^{-1}$ for RNA and protein conformational dynamics [44,48]. For barrier heights $\Delta G_{ij}^\ddagger \sim 5\text{--}15 \text{ kcal/mol}$, the resulting coupling amplitudes t_{ij} fall within the physically realistic regime required to describe spliceosomal conformational transitions.

The reduction in Eqs. (15) confirms that the spliceosomal conformational problem is a mathematically equivalent representation to an Anderson-type model. The consistency is verified by the correspondence in Table 2:

Table 2: Mathematical Correspondence Between Anderson Physics and Spliceosomal Biophysics

Feature	Anderson Physics (General Form)	Spliceosomal Biophysics
Lattice	Atomic positions in a crystal	Metastable conformational states $ i\rangle$
Disorder	Random impurity potential (W)	Parasite binding variance (σ_ϵ)
Transport	Electron conductivity	Conformational progression (splicing)
Hopping	Overlap Integral (V)	Transition coupling / "tunneling" ($\bar{t}$)
Measure	Inverse Participation Ratio (IPR)	Degree of state occupancy / trapping
Localization	Transition to Insulator	Functional Arrest (Kinetic Jamming)
Key Parameter	Ratio of Disorder to Hopping ($\frac{W}{t}$)	$\sigma_\epsilon / \bar{t}$

This correspondence provides the conceptual bridge between condensed matter physics and spliceosomal dynamics, enabling the application of Anderson localization theory to predict functional arrest under parasite-induced disorder.

Justification of the Mapping from Stochastic Dynamics to a Hermitian Tight-Binding Operator

While Eq. (13) defines an effective tight-binding Hamiltonian in terms of conformational energies and transition amplitudes, it is important to clarify the formal status of this construction. The spliceosomal system is fundamentally governed by classical stochastic dynamics rather than coherent quantum evolution. Therefore, we justify the introduction of a Hamiltonian operator to bridge the biomolecular kinetics and the Anderson-localization framework.

At coarse-grained resolution, spliceosomal conformational dynamics can be represented as a continuous-time Markov process over a discrete set of metastable conformational states, an approach widely used in the study of biomolecular dynamics through Markov state models (MSMs) and transfer operator formalisms[20,49-51]. In this representation, the probability vector $P(t)$ evolves according to the master equation:

$$\frac{dP_i(t)}{dt} = \sum_j K_{ij} P_j(t) \quad (16a)$$

where K_{ij} is the transition-rate matrix and satisfies the normalization condition $\sum_i K_{ij} = 0$, consistent with standard formulations of stochastic processes[52].

Under near-equilibrium conditions, the transition rates obey detailed balance with respect to the stationary distribution $\pi_i \propto e^{-\beta E_i}$, such that:

$$K_{ij}\pi_j = K_{ji}\pi_i \quad (16b)$$

This condition ensures reversibility of the stochastic dynamics and the existence of a well-defined equilibrium ensemble[53-54].

To obtain a symmetric representation, we introduce the similarity transformation:

$$\psi_i(t) = \pi_i^{-\frac{1}{2}} P_i(t) = e^{\frac{\beta E_i}{2}} P_i(t) \quad (16c)$$

which converts the master equation into a Hermitian imaginary-time evolution equation:

$$\frac{d\psi_i}{dt} = - \sum_j H_{ij}^{\text{eff}} \psi_j \quad (16d)$$

with the effective operator given by:

$$H_{ij}^{\text{eff}} = \begin{cases} -K_{ij}e^{\beta(E_i-E_j)/2}, & i \neq j, \\ \sum_{k \neq i} K_{ik}, & i = j \end{cases} \quad (16e)$$

By virtue of detailed balance, this operator satisfies $H_{ij}^{\text{eff}} = H_{ji}^{\text{eff}}$, and is therefore Hermitian. This transformation is a standard result in the theory of reversible Markov processes and guarantees real eigenvalues and a complete orthogonal eigenbasis[55].

The resulting operator has the same mathematical structure as a disordered tight-binding Hamiltonian, where heterogeneity in basin energies and transition barriers manifests as diagonal and off-diagonal disorder, while transition rates define effective couplings. Such mappings between stochastic dynamics and spectral operators are well-established in the study of disordered systems and relaxation processes[56-57]. Accordingly, the conformational transition network admits a rigorous spectral representation, enabling the application of Anderson-type localization theory to characterize the suppression of conformational accessibility. Importantly, this mapping pertains to the spectral properties of the stochastic generator, rather than implying literal quantum coherence in the underlying biomolecular system.

Analytical Significance and Disorder Threshold with Frustration

The Hamiltonian in Eq. (13) provides the formal input to the Time-Independent Schrödinger Equation governing conformational state accessibility. The spliceosomal conformational network is characterized by a low effective spectral dimension $d_s \approx 1.5-1.8$, placing it within the regime $d_s \leq 2$. In this regime, the scaling theory of localization predicts that disorder strongly suppresses delocalization, such that even moderate disorder can drive the system toward localized behavior. This is consistent with fractal-like descriptions of protein conformational space and network representations of biomolecular dynamics [20,48,58-60]. Consequently, conformational accessibility is highly sensitive to the ratio of disorder strength to coupling, $\sigma_\epsilon/\bar{t}$.

A critical distinction must be made between intrinsic frustration and parasite-induced disorder, which contribute additively but play fundamentally different roles. Intrinsic frustration, $\sigma_{\epsilon,\text{frust}} \approx 0.5-1.0$ kcal/mol, arises from evolutionarily conserved suboptimal interactions that enable conformational flexibility, allosteric communication, and multi-pathway sampling. This level of disorder is functional, as it prevents kinetic trapping while preserving the ability of the spliceosome to explore its conformational landscape and maintain catalytic fidelity[33,35]. In contrast, parasite-induced disorder, $\sigma_{\epsilon,\text{para}} \approx 2-5$ kcal/mol, represents pathological energetic heterogeneity introduced by exogenous RNA binding. These perturbations modify local basin depths and transition barriers in an inhomogeneous manner, effectively increasing the variance of on-site energies across the conformational network. The total disorder strength is therefore given by Eq.(8) ($\sigma_\epsilon^2 = \sigma_{\epsilon,\text{frust}}^2 + \sigma_{\epsilon,\text{para}}^2$).

Under native conditions ($\sigma_{\epsilon,\text{para}} = 0$), the system operates in a regime where $\sigma_\epsilon/\bar{t}$ remains below the effective localization threshold, allowing delocalized conformational dynamics and efficient catalytic progression. The intrinsic frustration thus provides controlled ruggedness without inducing arrest. However, as parasite-induced disorder increases, the ratio $\sigma_\epsilon/\bar{t}$ grows and eventually exceeds the critical value determined by the network's spectral dimension. At this point, the system undergoes a transition from a dynamically fluid regime to a localized regime, in which conformational trajectories become confined to a restricted subset of non-productive states.

This transition defines a functional disorder threshold, separating adaptive conformational flexibility from pathological dynamical arrest. The presence of intrinsic frustration implies that the system is already near the boundary of this transition, rendering it particularly susceptible to additional perturbations. Parasite RNA therefore acts as a control parameter that shifts the system across this threshold.

A key consequence of this framework is a quantitative and experimentally testable prediction: spliceosomal function should degrade progressively with increasing parasite RNA concentration, with a nonlinear or threshold-like transition occurring when the effective disorder strength satisfies

$$\frac{\sigma_\epsilon}{\bar{t}} \gtrsim \left(\frac{\sigma_\epsilon}{\bar{t}}\right)_{\text{crit}}(d_s) \quad (16f)$$

Beyond this point, localization dominates the conformational dynamics, suppressing access to catalytically competent states and resulting in functional arrest.

The disorder strength is computed from literature constraint parameters summarized in Table 3.

Table 3: **Frustration and Disorder Parameters**

Parameter	Symbol	Value / Range	Source
Intrinsic frustration (native)			
Frustration-induced energy variance	$\sigma_{\epsilon,\text{frust}}$	0.5–1.0 kcal/mol	[33,42]
Frustration magnitude at binding interfaces	ΔE_{frust}	1–3 kcal/mol	[33]
Parasite-induced disorder			
RNA binding energy	E_{bind}	5–15 kcal/mol	[38]
Conformational penalty	E_{pen}	3–8 kcal/mol	[39]
Parasite-induced variance	$\sigma_{\epsilon,\text{para}}$	2–5 kcal/mol	Derived from above
Total disorder			
Combined variance	σ_ϵ^2	$\sigma_{\text{frust}}^2 + \sigma_{\text{para}}^2$	Equation (8)
Total disorder strength	$\sigma_\epsilon/\bar{t}$	$\sim 1\text{--}5$	For $\bar{t} \approx 1\text{--}3$ kcal/mol

2.3. Solution of the TISE and Inverse Participation Ratio (IPR) Analysis

To determine the spatial extent of the spliceosomal conformational states under parasite-induced disorder, we solve the TISE for the tight-binding Hamiltonian defined in Eq. (13):

$$\hat{H}_{\text{TB}}|\psi_\alpha\rangle = E_\alpha|\psi_\alpha\rangle \quad (17)$$

where $|\psi_\alpha\rangle = \sum_i c_i^\alpha |i\rangle$ is the α -th conformational eigenstate and E_α is the corresponding eigenenergy. The coefficients c_i^α represent the probability amplitude of the spliceosome being in the i -th structural configuration.

Expanding in the local basis $\{|i\rangle$:

$$|\psi_\alpha\rangle = \sum_{i=1}^N \psi_\alpha(i) |i\rangle \quad (18)$$

where $\psi_\alpha(i)$ is the probability amplitude for conformational state i in eigenstate α . Substituting the tight-binding Hamiltonian from Eq. (13) yields the component form of the TISE:

$$\epsilon_i \psi_\alpha(i) + \sum_{j \in \text{nbr}(i)} t_{ij} \psi_\alpha(j) = E_\alpha \psi_\alpha(i) \quad (19)$$

For the simplest case of constant nearest-neighbour hopping $t_{ij} = t$ and a regular lattice of conformational states, this reduces to:

$$\epsilon_i \psi_\alpha(i) + t \sum_{j \in \text{nbr}(i)} \psi_\alpha(j) = E_\alpha \psi_\alpha(i) \quad (20)$$

Equation (20) is the discrete Schrödinger equation on a lattice. To see its equivalence to the standard Anderson model, we rewrite it as:

$$E_\alpha \psi_\alpha(i) = \epsilon_i \psi_\alpha(i) + t \sum_{j \in \text{nbr}(i)} \psi_\alpha(j)$$

In matrix form, for a one-dimensional chain of length N with nearest-neighbour hopping, this becomes:

$$E_\alpha \begin{pmatrix} \psi_\alpha(1) \\ \psi_\alpha(2) \\ \psi_\alpha(3) \\ \vdots \\ \psi_\alpha(N) \end{pmatrix} = \begin{pmatrix} \epsilon_1 & t & 0 & \cdots & 0 \\ t & \epsilon_2 & t & \cdots & 0 \\ 0 & t & \epsilon_3 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & t \\ 0 & 0 & 0 & t & \epsilon_N \end{pmatrix} \begin{pmatrix} \psi_\alpha(1) \\ \psi_\alpha(2) \\ \psi_\alpha(3) \\ \vdots \\ \psi_\alpha(N) \end{pmatrix} \quad (21)$$

Equation (21) is precisely the Anderson tight-binding Hamiltonian[24,27], with the following correspondence: the diagonal elements ϵ_i are the disordered on-site energies inherited from the perturbed Morse basins, the off-diagonal elements t are the nearest-neighbour conformational hopping amplitudes, and all remaining matrix elements vanish. Hence, the spliceosomal conformational problem reduces exactly to an Anderson-type eigenvalue problem, with disorder entering through the state-dependent energies ϵ_i .

For the spliceosomal conformational network, the on-site energies contain both intrinsic frustration and parasite-induced disorder:

$$\epsilon_i = \epsilon_i^{(0)} + \delta \epsilon_i^{(\text{frust})} + \delta \epsilon_i^{(\text{para})} \quad (22)$$

In the absence of disorder ($\sigma_\epsilon = 0$, $\epsilon_i = \epsilon_0$ constant), Eq.(20) admits plane wave solutions. For a d -dimensional hypercubic lattice:

$$c_i^{(k)} = \frac{1}{\sqrt{N}} e^{i\mathbf{k} \cdot \mathbf{r}_i} \quad (23)$$

with eigenenergies:

$$E_{\mathbf{k}} = \epsilon_0 + 2t \sum_{m=1}^d \cos(k_m a) \quad (24)$$

where a is the lattice spacing (characteristic conformational distance between neighbouring states) and $\mathbf{k}$ is the wavevector. These eigenstates are extended (delocalized), meaning the system can explore the full conformational landscape. The probability amplitude $|c_i^{(k)}|^2 = 1/N$ is uniformly distributed across all states. This regime corresponds to functional catalytic dynamics.

When disorder is present ($\sigma_\epsilon > 0$), the on-site energies ϵ_i become random variables. The eigenstates of Eq.(20) are no longer plane waves but become exponentially localized[24]. For a localized eigenstate centred at i_0 :

$$|c_i^{(\alpha)}| \sim \exp\left(-\frac{|i - i_0|}{\xi_\alpha}\right) \quad (25)$$

where ξ_α is the localization length of eigenstate α . This exponential confinement is the stationary-state signature of disorder-induced trapping in the spliceosomal conformational network.

The low effective spectral dimension of the spliceosomal conformational network ($d_s \approx 1.5-1.8 \leq 2$) places it in a regime where disorder strongly suppresses delocalization [59]. In such systems, even moderate disorder can drive the system toward localization, resulting in confinement of conformational dynamics.

To quantify the degree of localization, we compute the inverse participation ratio (IPR) of each eigenstate:

$$\text{IPR}_\alpha = |c_i^{(\alpha)}|^4 \quad (26)$$

The IPR distinguishes between different regimes as:

$$\text{IPR}_\alpha \sim \begin{cases} 1/N, & \text{delocalized states,} \\ \xi_\alpha^{-d_s}, & \text{localized states,} \\ 1, & \text{fully localized states.} \end{cases} \quad (27)$$

The average inverse participation ratio over all eigenstates is then

$$\langle \text{IPR} \rangle = \frac{1}{N} \sum_{\alpha=1}^N \text{IPR}_\alpha \quad (28)$$

In the delocalized regime, conformational eigenstates extend across the network, allowing efficient progression through catalytic states. In contrast, in the localized regime, eigenstates are confined to a small subset of configurations, preventing access to catalytically competent conformations. A finite value of $\langle \text{IPR} \rangle$ in the large- N limit indicates that the conformational eigenstates remain localized and that conformational exploration is restricted. Thus, disorder-induced localization provides a direct mechanistic link between parasite RNA binding and spliceosomal functional arrest. Increasing disorder reduces the localization length and increases the IPR, quantitatively capturing the collapse of conformational accessibility.

Localization Length, Disorder Threshold, and Quantitative Estimates

The spatial confinement of conformational eigenstates can be quantified through the **localization length** ξ , which characterizes the exponential decay of the eigenstate amplitudes in Eq. (25). For disordered tight-binding systems with diagonal disorder, analytical results from the one-dimensional Anderson model provide a tractable expression for the inverse localization length (Lyapunov exponent) [61-62]:

$$\xi^{-1} = \frac{1}{2} \ln \left(1 + \frac{\sigma_\epsilon^2}{4t^2} \right) \quad (29)$$

where σ_ϵ^2 is the variance of the on-site energy disorder and t is the nearest-neighbour hopping amplitude.

In the weak-disorder limit ($\sigma_\epsilon \ll t$), Eq. (29) reduces to

$$\xi \approx \frac{8t^2}{\sigma_\epsilon^2} \quad (30)$$

which explicitly shows that the localization length decreases quadratically with increasing disorder strength. This scaling is consistent with perturbative treatments of Anderson localization in low-dimensional systems[59,63].

For systems with effective spectral dimension $d_s \leq 2$, the scaling theory of localization predicts that disorder strongly suppresses delocalization and that extended states are not stable in the thermodynamic limit [59]. However, for finite systems such as biomolecular conformational networks, a practical disorder

threshold can be defined by the condition that the localization length becomes comparable to the system size N or to the number of functionally accessible states N_{eff} :

$$\xi \lesssim N_{\text{eff}} \quad (31)$$

We introduce the dimensionless disorder parameter

$$\Lambda = \frac{\sigma_\epsilon}{\bar{t}} \quad (32a)$$

functional arrest occurs when

$$\Lambda \gtrsim \Lambda_{\text{crit}} \sim \mathcal{O}(1) \quad (32b)$$

such that the localization length collapses to only a few conformational states. In low-dimensional and fractal networks, the effective critical threshold is small, implying that even moderate disorder can induce strong localization.

Numerical Estimates for Spliceosomal Parameters

Using the biophysically grounded parameters established in Section 2.2; Intrinsic frustration: $\sigma_{\epsilon, \text{frust}} \approx 0.5\text{--}1.0$ kcal/mol, Parasite-induced disorder $\sigma_{\epsilon, \text{para}} \approx 2\text{--}5$ kcal/mol, Total disorder $\sigma_\epsilon = \sqrt{\sigma_{\epsilon, \text{frust}}^2 + \sigma_{\epsilon, \text{para}}^2} \approx 2.1\text{--}5.1$ kcal/mol, Hopping amplitude $\bar{t} \approx 1\text{--}3$ kcal/mol, we obtain the disorder ratio

$$\Lambda = \frac{\sigma_\epsilon}{\bar{t}} \approx 0.7\text{--}5$$

Substituting into Eq. (29), for representative values $\sigma_\epsilon/t \sim 1$,

$$\xi^{-1} \approx \frac{1}{2} \ln(1.25) \approx 0.111, \Rightarrow \xi \approx 9$$

For stronger disorder ($\sigma_\epsilon/t \sim 2\text{--}3$),

$$\xi^{-1} \approx \frac{1}{2} \ln\left(1 + \frac{4-9}{4}\right) \approx 0.3\text{--}0.6, \Rightarrow \xi \approx 2\text{--}3.$$

Thus, under biologically realistic perturbations, the localization length decreases from a regime where multiple conformational states are accessible ($\xi \sim 5\text{--}10$) to a regime where only a few states are accessible ($\xi \sim 1\text{--}3$). This collapse in localization length directly corresponds to a loss of conformational flexibility and catalytic accessibility.

The reduction in localization length is accompanied by a corresponding increase in the inverse participation ratio. Using the scaling relation $\text{IPR} \sim \xi^{-d_s}$ with $d_s \approx 1.5\text{--}1.8$, we obtain:

Weak disorder ($\xi \sim 10$):

$$\text{IPR} \sim 10^{-1.5} \approx 0.03$$

Strong disorder ($\xi \sim 2$):

$$\text{IPR} \sim 2^{-1.5} \approx 0.35$$

This represents an order-of-magnitude increase in IPR, indicating strong confinement of conformational eigenstates.

These results demonstrate that parasite-induced disorder is sufficient to drive the spliceosomal conformational network across a functional threshold, where localization length collapses and eigenstates become confined to a small subset of non-productive configurations. The combination of reduced ξ and increased IPR provides a quantitative signature of disorder-induced functional arrest.

2.4. Spectral Dynamics of the Symmetrized Rate Operator and Localization Signatures

To characterize the dynamical propagation of conformational states across the spliceosomal network, we analyze the spectral properties of the symmetrized rate operator introduced in Section 2.2. While the physical dynamics are governed by the classical master equation

$$\frac{dP(t)}{dt} = KP(t) \quad (33)$$

it is mathematically convenient to express the evolution in terms of a Hermitian operator H_{eff} , obtained via similarity transformation under detailed balance. This transformation, widely used in the analysis of reversible stochastic processes, maps the generator of a Markov process to a symmetric operator with real eigenvalues and orthogonal eigenvectors[53,55]. The resulting dynamics can be written in a Schrödinger-like form in imaginary time:

$$-\hbar \frac{\partial}{\partial t} |\psi(t)\rangle = H_{\text{eff}} |\psi(t)\rangle \quad (34)$$

where $|\psi(t)\rangle$ is related to the probability vector $P(t)$ through the transformation defined in Section 2.2. This formulation does not imply physical quantum coherence; rather, it reflects the well-established algebraic equivalence between reversible Markov processes and imaginary-time evolution under a Hermitian operator[52,55].

Expanding the state vector in the eigenbasis of H_{eff} :

$$|\psi(t)\rangle = \sum_{\alpha} c_{\alpha} e^{-E_{\alpha}t/\hbar} |\psi_{\alpha}\rangle \quad (35)$$

where $|\psi_{\alpha}\rangle$ and E_{α} are the eigenstates and eigenvalues of H_{eff} . This representation is mathematically equivalent to the spectral decomposition of the master equation propagator and is commonly employed in the analysis of relaxation dynamics in complex stochastic systems[57].

Unlike real-time quantum evolution, the dynamics are purely dissipative that is, modes with larger eigenvalues decay rapidly, while long-time behavior is dominated by low-energy eigenmodes. This hierarchy of relaxation times is a standard feature of Markovian systems and underlies the emergence of slow collective conformational modes in biomolecular dynamics[20,51]. Specifically, the largest relaxation time t_{eq} governing convergence to equilibrium is given by $t_{\text{eq}} = 1/E_1$, where E_1 is the first non-vanishing eigenvalue of H^{eff}

To probe transport properties, we consider an initial condition corresponding to a localized conformational state $c_i(0) = \delta_{i,i_0}$, representing a spliceosome initially confined to configuration i_0 .

The time-dependent coefficients evolve as:

$$c_i(t) = \sum_{\alpha} e^{-E_{\alpha}t/\hbar} c_i^{(\alpha)} c_{i_0}^{(\alpha)*} \quad (36)$$

Eq.(36) describes the redistribution of probability across conformational states and reflects the contribution of each eigenmode to the overall dynamics.

The extent of conformational exploration is quantified by the mean-square displacement (MSD):

$$\langle r^2(t) \rangle = \sum_i |r_i - r_{i_0}|^2 |c_i(t)|^2 \quad (37)$$

In the absence of strong disorder, eigenstates are extended across the conformational network, leading to increasing MSD and efficient exploration of configurational space. In contrast, in the presence of disorder, eigenstates become spatially localized, and the MSD saturates at long times:

$$\lim_{t \rightarrow \infty} \langle r^2(t) \rangle \sim \xi^2 \quad (38)$$

where ξ is the localization length. This saturation reflects restricted conformational accessibility and is consistent with established results for disordered systems, where localization suppresses transport and diffusion[56,57]. This behavior is characteristic of Anderson-localized systems, where the eigenstates of the tight-binding Hamiltonian are exponentially localized.

Temporal Signatures of Localization

A direct signature of localization is provided by the return probability:

$$P_{i_0}(t) = |c_{i_0}(t)|^2 \quad (39)$$

In the delocalized regime:

$$P_{i_0}(t) \rightarrow \frac{1}{N}, t \rightarrow \infty,$$

indicating uniform exploration of the conformational network. In contrast, in the localized regime:

$$P_{i_0}(t) \rightarrow \text{finite value} > 0,$$

demonstrating persistent confinement near the initial state. Such behavior is characteristic of systems with localized eigenstates and reflects the suppression of long-range transitions[57].

The quantities defined above viz the mean-square displacement, return probability, and eigenstate localization should be interpreted as spectral properties of the symmetrized rate operator, rather than as manifestations of physical quantum dynamics. Localization of eigenstates implies that probability flow is confined to a restricted subset of conformational states. In the context of spliceosomal dynamics, this corresponds to a breakdown of global connectivity within the conformational network, preventing access to catalytically competent configurations.

Thus, parasite-induced energetic disorder drives a transition from a delocalized regime, characterized by efficient conformational sampling, to a localized regime, where dynamics are restricted and functional progression is arrested. This interpretation aligns with established theoretical frameworks for disorder-induced localization in complex networks and disordered systems[56,64].

Decoherence and Transition to Classical Dynamics

In biological environments, interactions with the surrounding solvent and macromolecular environment induce rapid decoherence on femtosecond-to-picosecond timescales (10^{-13} – 10^{-12} s)[43]. In this regime, the coherent evolution transitions to an incoherent hopping process between localized eigenstates.

The transition rate between eigenstates $\alpha \rightarrow \beta$ is given by Fermi's Golden Rule:

$$k_{\alpha \rightarrow \beta} = \frac{2\pi}{\hbar} |\langle \psi_\beta | V_{\text{env}} | \psi_\alpha \rangle|^2 \rho(E_\beta) \quad (40)$$

where V_{env} represents coupling to environmental degrees of freedom and $\rho(E_\beta)$ is the density of final states. This expression is used as a formal analogy to describe transition rates between localized modes; physically, it corresponds to thermally activated hopping rates in a dissipative environment.

Because eigenstates are localized, these transition rates decay exponentially with distance:

$$k_{\alpha \rightarrow \beta} \propto \exp\left(-\frac{|r_{\alpha} - r_{\beta}|}{\xi}\right) \quad (41)$$

where $\mathbf{r}_{\alpha}$ and $\mathbf{r}_{\beta}$ are the centres of localization. This suppression of transition rates is the dynamical signature of Anderson localization: the system becomes trapped in a limited subset of conformational states, unable to access the catalytically competent regions of the landscape.

The spectral analysis of the symmetrized rate operator reveals the dynamical consequences of localization. In the delocalized regime, probability amplitudes extend across the conformational network, enabling efficient transitions between catalytic states. In contrast, in the localized regime, these amplitudes remain spatially confined, preventing access to distant conformational states. Thus, parasite-induced disorder transforms the spliceosome from a dynamically exploring system into one characterized by confined probability flow and kinetic trapping. This provides a time-resolved mechanism for functional arrest: localization of eigenstates suppresses the redistribution of probability across the network, leading to long-lived occupation of non-productive conformational states.

2.5. Mapping Disorder-Induced Localization to Functional Occupancy

We consider a conformational network consisting of N discrete states, with a subset $C \subseteq \{1, \dots, N\}$ corresponding to catalytically competent configurations. The functional occupancy is defined as

$$P_{\text{func}}(t) = \sum_{i \in C} P_i(t) \quad (42)$$

where $P_i(t)$ is the probability of occupying state i at time t . This definition follows directly from coarse-grained descriptions of biomolecular function, where functional output is determined by the occupancy of specific conformational substates within a Markov state model framework[49,50].

Under the similarity transformation $\psi_i(t) = \pi_i^{-1/2} P_i(t)$, introduced in Section 2.3, the dynamics are expressed in terms of the eigenstates $\psi_{\alpha}(i)$ of the symmetrized rate operator. The long-time behavior is governed by the spectral decomposition of this operator, such that the spatial support of its eigenstates determines the effective number of accessible conformational states [51,55].

In the delocalized regime, eigenstates are extended over the full conformational network, yielding

$$|\psi_{\alpha}(i)|^2 \sim \frac{1}{N}, \Rightarrow P_{\text{func}} \approx \frac{|C|}{N} \quad (43)$$

Here $|C|$ is the number of catalytically competent states. This scaling reflects ergodic exploration of the state space, consistent with equilibrium sampling in reversible Markov processes satisfying detailed balance[52,54].

In the high-disorder regime ($\Lambda \gtrsim 1$), eigenstates are confined to a subset of size on the order of the localization length ξ . The effective number of accessible states is therefore reduced from N to $\sim \xi$, and the functional probability becomes

$$P_{\text{func}} \sim \frac{|C \cap \xi|}{\xi} \quad (44a)$$

where $|C \cap \xi|$ denotes the number of catalytically competent states within the localized region. Since localization restricts the spatial extent of eigenstates independently of the location of catalytically competent states, the probability that the localized region overlaps with C decreases with increasing disorder. Averaging over disorder realizations, the functional probability scales as

$$P_{\text{func}} \propto \frac{\xi}{N} \quad (44b)$$

Eq.(44b) provides a direct bridge between the localization length and catalytic accessibility.

This reduction in effective state space is consistent with coarse-graining approaches in biomolecular kinetics, where low-occupancy or inaccessible states are effectively removed from the dynamics, leading to reduced functional accessibility[53].

The localization length ξ depends on the ratio of coupling strength $V \sim \bar{t}$ to disorder amplitude $W \sim \sigma_\epsilon$. In the weak-to-intermediate disorder regime, it follows the scaling relation

$$\xi \propto \frac{\bar{t}^2}{\sigma_\epsilon^2} \propto \frac{V^2}{W^2} \quad (45)$$

which arises from perturbative treatments of disordered systems and has been extensively established in studies of Anderson localization and related stochastic models [56,57].

Substituting Eq. (45) into Eq. (44) yields

$$P_{\text{func}}(W) \approx P_{\text{func}}(0) \left(\frac{V^2}{W^2} \right) \quad (46)$$

valid up to the regime where $\xi \ll N$. This expression predicts a rapid suppression of catalytic accessibility with increasing disorder strength, scaling as W^{-2} .

An equivalent representation can be formulated in terms of the inverse participation ratio,

$$\text{IPR} = \sum_i |\psi_\alpha(i)|^4 \quad (47)$$

which quantifies the degree of eigenstate localization. For localized states, the scaling $\text{IPR} \sim \frac{1}{\xi}$ holds, leading to

$$P_{\text{func}} \propto \frac{1}{N \cdot \text{IPR}} \quad (48)$$

The use of IPR as a localization metric is standard in disordered systems and provides a direct measure of the effective number of contributing states[57]

Experimental Predictions: Splicing Efficiency

To connect these quantities to experimentally measurable observables, we define the effective splicing efficiency η as the fraction of pre-mRNA transcripts successfully processed per unit time. Assuming that catalytic activity is proportional to the probability of occupying functional states, we define the splicing efficiency η as proportional to the functional occupancy,

$$\eta(W) = \eta_0 P_{\text{func}}(W) \quad (49)$$

where η_0 is the efficiency in the absence of parasite-induced perturbation. Substituting the scaling relation from Eq. (46)

$$\eta(W) \approx \eta_0 \left(\frac{V^2}{W^2} \right) \quad (50)$$

which predicts a power-law decay of splicing efficiency with increasing disorder strength, $\eta \sim W^{-2}$

In the strong-disorder regime, where higher-order corrections become significant and the system enters the strongly localized regime ($\xi \sim 1-2$), this dependence is well approximated by an exponential form

$$P_{\text{func}}(W) \sim \exp\left(-\alpha \frac{W^2}{V^2}\right) \quad (51)$$

leading to

$$\eta(W) \approx \eta_0 \exp\left(-\alpha \frac{W^2}{V^2}\right) = \eta_0 \exp(-\alpha \Lambda^2) \quad (52)$$

where α is a dimensionless constant of order unity capturing network topology and dimensionality effects, and $\Lambda = \sigma_\epsilon/\bar{t}$ is the dimensionless disorder parameter defined in Eq. (32a). This expression provides a quantitative prediction linking parasite-induced energetic disorder to functional impairment. This exponential suppression reflects the general behavior of transport and accessibility in strongly disordered systems with localized eigenstates[65].

Dynamically, the restriction of eigenstate support implies saturation of the mean-square displacement,

$$\langle r^2(t \rightarrow \infty) \rangle \sim \xi^2 \quad (53)$$

and a finite long-time return probability,

$$P_{i_0}(\infty) = \sum_{\alpha} |\psi_{\alpha}(i_0)|^4 \sim \text{IPR} \quad (54)$$

These relations follow directly from the spectral representation of reversible Markov processes and are consistent with known results on relaxation and confinement in disordered stochastic systems[51,55]. Equations (43)–(54) therefore establish a quantitative mapping between disorder-induced localization and functional occupancy in the spliceosomal conformational network, linking spectral properties of the rate operator to measurable functional outcomes.

2.6. Limit of Validity of the Anderson-Type Mapping

The applicability of the Anderson-type mapping is constrained by several assumptions inherent to the coarse-grained stochastic representation. Each assumption defines a regime within which the mapping is quantitatively meaningful; outside these regimes, the framework requires extension.

1. Timescale Separation and Markovianity

A fundamental requirement of the present framework is that conformational dynamics can be coarse-grained into memoryless transitions between metastable states. This is valid only when there is a clear separation between fast intra-state relaxation and slower inter-state transitions, such that:

$$\tau_{\text{fast}} \ll \tau_{\text{slow}},$$

where τ_{fast} characterizes local vibrational and conformational fluctuations (picoseconds to nanoseconds) and τ_{slow} characterizes transitions between metastable states (microseconds to seconds). Under this condition, the dynamics are effectively Markovian and can be described by a master equation.

When this separation breaks down ($\tau_{\text{fast}} \sim \tau_{\text{slow}}$), memory effects become significant and the dynamics are no longer Markovian. In such cases, the master equation must be replaced by generalized Langevin or memory kernel formulations, such as those derived from the Mori–Zwanzig projection formalism. This assumption underlies Markov state modeling and transfer operator approaches in biomolecular systems[20,51].

2. Detailed Balance and Near-Equilibrium Conditions

The mapping to a Hermitian operator requires that the transition rates satisfy detailed balance:

$$K_{ij}\pi_j = K_{ji}\pi_i, \pi_i \propto e^{-\beta E_i}$$

This condition implies that the system operates near equilibrium, with no net probability currents in the stationary state. Under these conditions, the stochastic generator can be symmetrized via similarity transformation, yielding a Hermitian operator with real eigenvalues.

However, the spliceosome is an active molecular machine driven by ATP hydrolysis, and thus may operate away from strict equilibrium. Deviations from detailed balance can be quantified by a non-equilibrium measure:

$$\theta = \frac{1}{2} \frac{\sum_{i,j} (K_{ij}\pi_j - K_{ji}\pi_i)^2}{\sum_{i,j} K_{ij} \pi_j},$$

which vanishes under equilibrium conditions. This quantity is analogous to entropy production-based measures of detailed-balance violation in stochastic thermodynamics[65].

When $\theta > 0$, the rate matrix cannot be fully symmetrized, and the effective operator becomes non-Hermitian. In such cases, the present framework must be extended to non-equilibrium spectral theories, including non-Hermitian operator analysis or Fokker–Planck descriptions with non-conservative forces[65].

3. Classical Stochastic vs. Quantum Coherent Dynamics

The Schrödinger-like equation derived in Section 2.4,

$$\frac{d\psi_i}{dt} = - \sum_j H_{ij}^{\text{eff}} \psi_j,$$

represents an imaginary-time evolution equation, not real-time quantum dynamics. The absence of the factor i reflects the dissipative, non-unitary nature of the evolution.

This mapping is purely algebraic and arises from the transformation of a reversible Markov process into a symmetric operator representation. It does not imply physical quantum coherence or wavefunction dynamics. Instead, the operator H_{eff} generates a semigroup evolution $e^{-H_{\text{eff}}t/\hbar}$, describing relaxation rather than coherent propagation[55].

No experimentally supported regime exists in which spliceosomal conformational dynamics exhibit long-lived quantum coherence on the millisecond-to-second timescales relevant for splicing. Environmental interactions in biomolecular systems induce rapid decoherence on femtosecond to picosecond timescales, ensuring that conformational dynamics remain effectively classical.

4. Effective Spectral Dimension and the Localization Threshold

The emergence of localization depends critically on the effective spectral dimension d_s of the conformational network. According to the scaling theory of localization:

$$\lambda_c = 0 \text{ for } d_s \leq 2, \lambda_c > 0 \text{ for } d_s > 2,$$

where $\lambda_c = (\sigma_\epsilon/\bar{t})_c$ is the critical disorder strength.

Protein conformational landscapes are widely characterized by low effective dimensionality and fractal-like organization, with estimates typically in the range $d_s \approx 1.5 - 1.8$, consistent with reduced-dimensional representations of biomolecular dynamics[20,51]. In this regime, even moderate disorder can induce localization.

If the conformational network were instead highly connected or effectively higher-dimensional, the localization threshold would become finite, and weak disorder might not suppress transport. In such cases, functional arrest would require:

$$\frac{\sigma_\epsilon}{\bar{t}} > \lambda_c(d_s),$$

where $\lambda_c(d_s)$ increases with d_s [64].

5. Quenched vs. Annealed Disorder

The present framework assumes that disorder is quenched, meaning that perturbations such as parasite RNA binding remain effectively static over the timescale of conformational transitions:

$$\frac{d\epsilon_i}{dt} \approx 0 \text{ for } t \lesssim \tau_{\text{slow}}.$$

Under this assumption, disorder acts as a fixed modification of the energy landscape, enabling localization. If the perturbation fluctuates rapidly (annealed disorder), the effective disorder strength is averaged over time:

$$\sigma_{\epsilon, \text{eff}}^2 = \int_0^\infty \langle \delta \epsilon_i(0) \delta \epsilon_i(t) \rangle dt.$$

When the fluctuation timescale $\tau_{\text{fluct}} \ll \tau_{\text{slow}}$, disorder averages out, restoring ergodic exploration and suppressing localization effects. The ratio $\tau_{\text{fluct}}/\tau_{\text{slow}}$ therefore defines the crossover between quenched and annealed regimes [57].

For the spliceosome, parasite RNA binding is stable on the timescale of splicing, justifying the quenched approximation.

6. Finite-Size Effects

Localization measures such as the inverse participation ratio (IPR) and localization length ξ are strictly defined in the thermodynamic limit ($N \rightarrow \infty$). For finite conformational networks ($N \sim 10^3 - 10^4$), finite-size effects become important.

Localization is observable when:

$$\xi \ll L,$$

where L is the characteristic size of the network. When $\xi \sim L$, the distinction between localized and delocalized states becomes ambiguous.

In this regime, localization measures exhibit finite-size scaling:

$$\langle \text{IPR} \rangle \sim N^{-\tau(d_s)},$$

where $\tau(d_s) \rightarrow 0$ in the localized limit. For the purposes of the present work, we focus on qualitative localization behavior rather than precise critical scaling. A full finite-size scaling analysis may be required for quantitative determination of localization thresholds [64]. The validity regimes are summarized in table 4:

Table 4: Summary of Validity Regimes

Assumption	Valid Regime	Breakdown	Required Extension
Timescale separation	$\tau_{\text{fast}} \ll \tau_{\text{slow}}$	$\tau_{\text{fast}} \sim \tau_{\text{slow}}$	Non-Markovian dynamics
Detailed balance	$\theta = 0$	$\theta > 0$	Non-Hermitian spectral theory
Classical dynamics	$\hbar/k_B T \ll \tau_{\text{slow}}$	Not applicable	Purely classical
Spectral dimension	$d_s \leq 2$	$d_s > 2$	Finite threshold $\lambda_c(d_s)$
Disorder type	$\tau_{\text{fluct}} \gg \tau_{\text{slow}}$	$\tau_{\text{fluct}} \ll \tau_{\text{slow}}$	Annealed averaging

System size	$\xi \ll L$	$\xi \sim L$	Finite-size scaling
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Within these constraints, the Anderson-type mapping provides a quantitatively meaningful description of disorder-induced suppression of conformational accessibility. Outside these regimes, extensions incorporating non-Markovian dynamics, non-equilibrium driving, or time-dependent disorder may be required.

2.7. Computational Implementation

To test the analytical predictions of Sections 2.2–2.3, we implement numerical simulations of the disordered tight-binding model on a finite conformational network. The spliceosomal conformational space is represented as a graph $G = (V, E)$ with $N = 10^3$ – 10^4 nodes, each corresponding to a distinct structural configuration obtained from cryo-EM ensembles or molecular dynamics trajectories[14,15]. Connectivity between states is defined using a conformational distance cutoff of $\ell_c \approx 3$ – 7 Å, ensuring that only structurally adjacent configurations are coupled.

Disorder is introduced by sampling the on-site energies ϵ_i from a Gaussian distribution with variance determined by the combined effects of intrinsic frustration and parasite-induced perturbation. The strength of parasite-induced disorder is treated as a control parameter and varied systematically to probe the transition from functional to arrested regimes.

For each realization of disorder, the Hamiltonian matrix is constructed and numerically diagonalized to obtain the eigenvalues and eigenstates. From these, the inverse participation ratio and localization length are computed using the definitions established in Section 2.3. Dynamical behavior is evaluated by propagating an initially localized state and computing observables such as mean-square displacement and return probability.

All quantities are averaged over $\sim 10^3$ independent disorder realizations to ensure statistical convergence. Convergence with respect to system size N and ensemble averaging is verified by monitoring the average IPR as a function of N ; observed trends are confirmed not to be finite-size artifacts. All computations are performed using custom-developed scripts in the Python programming language, utilizing the NumPy and SciPy libraries for matrix diagonalization and numerical propagation. The full source code used for the simulations is provided as supplementary material to ensure reproducibility.

This numerical framework directly tests the central prediction of the model: that increasing disorder strength drives a transition from delocalized conformational dynamics to a localized regime characterized by restricted state accessibility and functional arrest.

3.0. RESULTS AND DISCUSSION

The results of the computation and analysis of the Eqs. (1)-(54) formulated in the Method section is presented here. The python code used for the computation and visualization is <https://github.com/Udoisohm/Disorder-induced-localization/releases/new>

Figure 4 presents the effective conformational energy landscape $V_{\text{eff}}(q)$ constructed from a superposition of Morse-type potentials representing metastable spliceosomal configurations. The reaction coordinate $q(\text{Å})$ parametrizes collective structural degrees of freedom extracted from coarse-grained conformational modes.

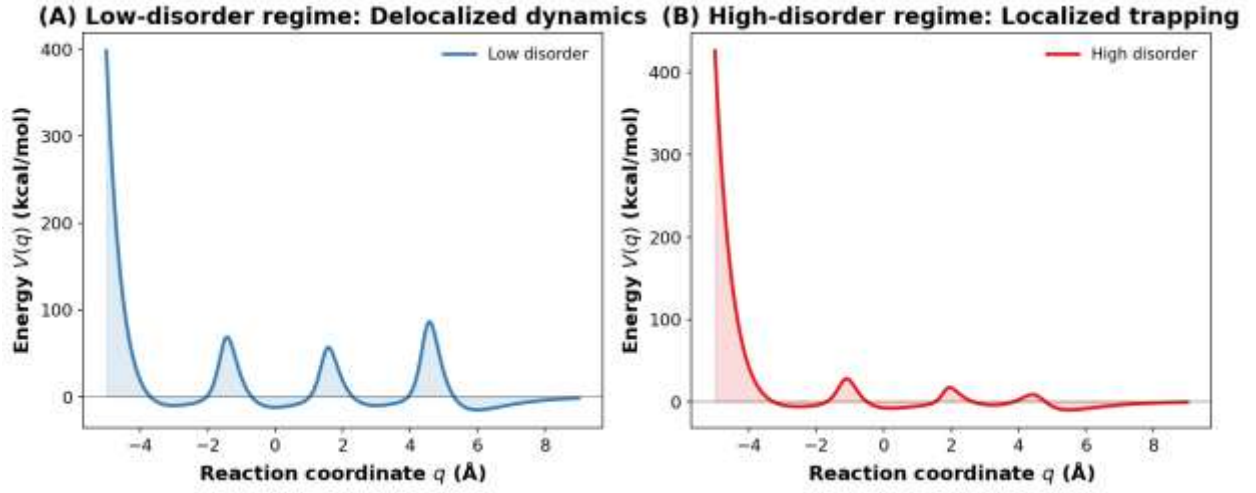


Figure 4 | Effective Conformational Energy Landscape Under Disorder

Panel (A) shows the low-disorder regime, corresponding to the native spliceosomal system, where intrinsic energetic frustration dominates. Panel (B) shows the high-disorder regime, where parasite-induced perturbations modify basin depths and barrier heights. The energy scale is expressed in kcal/mol, allowing direct comparison with thermal energy $k_B T \approx 0.6$ kcal/mol at physiological conditions.

In the low-disorder regime shown in Figure 4(A), the energy landscape exhibits a series of well-defined minima separated by relatively high and smooth energy barriers. The barrier heights are on the order of $\Delta G_{ij}^\ddagger \sim 10-15$ kcal/mol, significantly exceeding thermal energy, which ensures that transitions between conformational states are activated and occur with well-defined rates. The basins are approximately symmetric and regularly spaced along the reaction coordinate, reflecting an organized and weakly frustrated conformational landscape. In contrast, the high-disorder regime shown in Figure 4(B) is characterized by a substantial reduction in barrier heights to $\Delta G_{ij}^\ddagger \sim 3-8$ kcal/mol, accompanied by pronounced irregularity in basin depths and positions. The resulting landscape is markedly rough, with asymmetric wells and non-uniform spacing, indicating the presence of strong energetic disorder and frustration.

This trend arises from the perturbation of the Morse potential parameters that define the individual conformational basins. The effective landscape can be expressed as $V_{\text{eff}}(q) = \sum_i D_i (1 - e^{-a_i(q-q_i)})^2 + \delta V_{\text{para}}(q)$, where D_i determines the well depth, a_i controls the curvature and barrier sharpness, and $\delta V_{\text{para}}(q)$ represents parasite-induced energetic fluctuations. In the high-disorder regime, variations in D_i and a_i lead to heterogeneous barrier heights, while random shifts in the equilibrium positions q_i introduce spatial disorder in the locations of minima. These effects increase the variance of the on-site energies $\epsilon_i = V_{\text{eff}}(q_i)$, such that the total disorder strength satisfies $\sigma_\epsilon^2 = \sigma_{\text{frust}}^2 + \sigma_{\text{para}}^2$. Simultaneously, the reduction in barrier heights enhances the inter-state coupling amplitudes $t_{ij} \sim \exp(-\Delta G_{ij}^\ddagger / 2k_B T)$, thereby modifying both diagonal and off-diagonal elements of the corresponding tight-binding representation.

The observed transformation is consistent with established theoretical descriptions of biomolecular energy landscapes and disordered systems. In protein energy landscape theory, functional biomolecules are known to operate on structured but rugged landscapes, while increased disorder leads to enhanced frustration and trapping in metastable states [66]. Similarly, in stochastic descriptions of biomolecular conformational dynamics, perturbations to state energies and transition barriers are known to induce slow relaxation and restricted configurational exploration [20,50]. More broadly, in statistical mechanics

of disordered systems, increasing heterogeneity in the potential landscape is associated with the emergence of localization-like behavior and constrained dynamics[65]. The transition from the smooth, structured landscape in Figure 4(A) to the heterogeneous landscape in Figure 4(B) therefore reflects a general physical principle linking disorder to dynamical restriction.

The results imply that parasite-induced perturbations introduce a systematic increase in energetic disorder within the spliceosomal conformational landscape, which directly translates into an increase in the disorder parameter $\Lambda = \sigma_\epsilon/\bar{t}$. This provides the microscopic basis for mapping the system onto a disordered tight-binding model, where the basin energies $V_{\text{eff}}(q_i)$ define the on-site energies and the barrier-dependent transition amplitudes define the hopping integrals. As Λ increases, the system is driven toward the regime where localization effects dominate, restricting conformational accessibility.

Figure 5 quantifies the emergence of disorder-induced localization through two complementary metrics derived from the tight-binding representation of the conformational network.

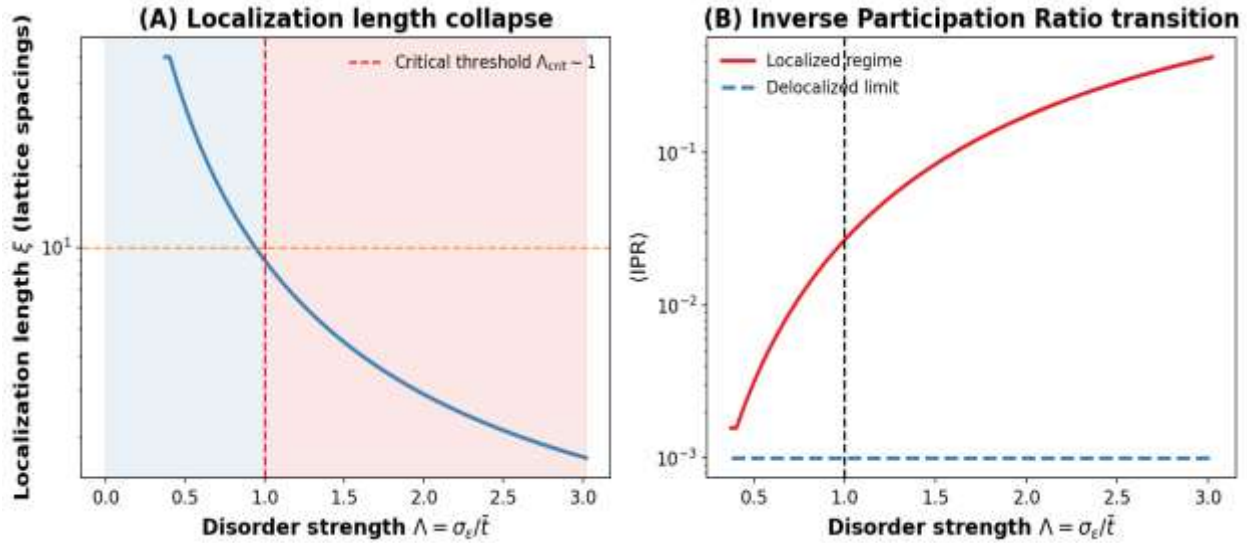


Figure 5 | Localization Length Collapse and Inverse Participation Ratio Transition

Panel (A) shows the localization length ξ as a function of the disorder ratio $\Lambda = \sigma_\epsilon/\bar{t}$, while panel (B) presents the corresponding inverse participation ratio (IPR), defined as $\text{IPR} = \sum_i |\psi_\alpha(i)|^4$, which measures the spatial concentration of eigenstates. The disorder ratio is normalized by the mean hopping amplitude $\bar{t}$, allowing direct comparison across regimes, and the critical threshold $\Lambda_{\text{crit}} \sim 1$ is indicated in both panels.

In Figure 5(A), the localization length ξ exhibits a sharp monotonic decrease with increasing disorder strength. Specifically, ξ decreases from values exceeding 10^2 lattice spacings in the low-disorder regime ($\Lambda < 0.5$) to values on the order of unity as $\Lambda \rightarrow 2-3$. This rapid collapse indicates a transition from extended eigenstates that span the entire conformational network to strongly localized states confined to a few neighboring configurations. In Figure 5(B), the IPR shows the complementary behavior, increasing from values near 10^{-3} , characteristic of delocalized states with uniform amplitude distribution over $N \sim 10^2-10^3$ states, to values exceeding 10^{-1} in the high-disorder regime. The transition occurs near $\Lambda \sim 1$, where the slope of the IPR curve increases markedly, signaling the onset of localization.

This trend arises from the exponential sensitivity of eigenstate spatial extent to the ratio of disorder strength to coupling amplitude in disordered lattice systems. From the analytical expression derived for the localization length in Eq.(29), it follows that even moderate increases in σ_ϵ produce a logarithmic increase in the denominator, leading to a rapid reduction in ξ . Physically, increasing disorder introduces fluctuations in the on-site energies ϵ_i , which disrupt coherent coupling between neighboring states and

suppress long-range amplitude propagation. As a result, eigenstates become exponentially localized with spatial profiles $|\psi_\alpha(i)|^2 \sim \exp(-|i - i_0|/\xi)$. The inverse participation ratio, being proportional to the inverse of the effective number of occupied sites, scales as $\text{IPR} \sim \xi^{-1}$ in one-dimensional systems, thereby increasing as localization strengthens.

This result is consistent with the scaling theory of Anderson localization, which predicts that in one-dimensional systems, all eigenstates become localized for any finite disorder, with the localization length decreasing continuously as disorder increases[59]. The sharp crossover near $\Lambda \sim 1$ observed here corresponds to a practical localization threshold where the localization length becomes comparable to the system size. Similar trends have been reported in studies of disordered quantum and stochastic systems, where the inverse participation ratio serves as a robust indicator of localization transitions[57]. In the context of biomolecular dynamics, analogous measures have been used to characterize restricted conformational sampling and metastability in Markov state models [20,50], supporting the interpretation of increased IPR as a signature of reduced configurational accessibility.

The results imply that the increase in disorder induced by parasite interaction is sufficient to drive a collapse of the localization length to the scale of a few conformational states, effectively confining the system to a limited region of its conformational network. This confinement manifests as a dramatic increase in the inverse participation ratio, indicating that only a small subset of states contributes significantly to the system's dynamics. Consequently, the spliceosome transitions from a regime of global conformational exploration to one of localized, kinetically trapped dynamics. This provides a quantitative mechanism linking molecular-scale perturbations to functional impairment, as the inability to access distant conformational states directly translates into a loss of catalytic flexibility. This result thus establishes the central quantitative result of the study: that parasite-induced disorder drives a localization transition in the conformational network, forming the basis for the dynamical arrest explored in subsequent figures.

Figure 6 presents the disorder-driven localization transition in the spliceosomal conformational network, quantified through the average inverse participation ratio $\langle \text{IPR} \rangle$ as a function of the normalized disorder strength $\Lambda = \sigma_\epsilon/t$.

Anderson localization transition in the spliceosomal network

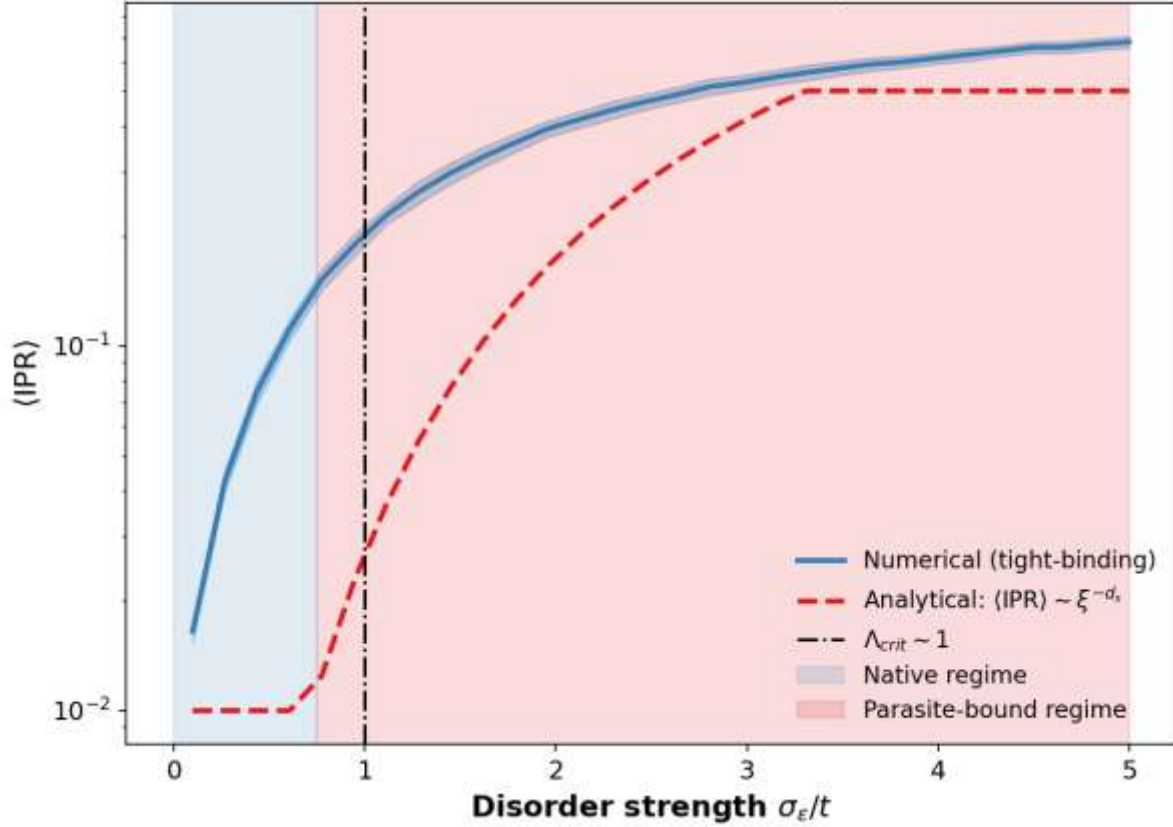


Figure 6. Anderson Localization Transition in the Spliceosomal Conformational Network

The solid blue curve represents numerical results obtained from diagonalization of the tight-binding Hamiltonian in Eq. (13), while the red dashed curve shows the analytical scaling relation $\langle \text{IPR} \rangle \sim \xi^{-d_s}$, where ξ is the localization length and d_s is the effective spectral dimension. The vertical dashed line marks the critical disorder threshold $\Lambda_{\text{crit}} \sim 1$, separating the native (delocalized) regime from the parasite-bound (localized) regime, which are highlighted by shaded regions.

The numerical results exhibit a clear monotonic increase in $\langle \text{IPR} \rangle$ with increasing disorder strength. In the low-disorder regime ($\Lambda < 0.5$), the IPR remains small, on the order of $\sim 10^{-2}$, indicating that eigenstates are extended across a large fraction of the conformational network. As the disorder increases toward the critical region ($\Lambda \approx 1$), the IPR rises rapidly, reaching values $\sim 10^{-1}$, and continues to increase gradually in the high-disorder regime, where it approaches a plateau. This behavior reflects a transition from delocalized eigenstates, which sample many conformational configurations, to localized states confined to a small subset of states. The analytical curve reproduces this trend, capturing both the rapid growth near the threshold and the saturation behavior at higher disorder.

This trend arises from the interplay between energetic disorder and inter-state coupling in the tight-binding representation. As the variance of the on-site energies σ_ϵ increases relative to the hopping amplitude t , fluctuations in ϵ_i disrupt coherent coupling between neighboring states, leading to spatial confinement of eigenstates. The localization length ξ , which governs the spatial extent of the eigenstates, decreases according to $\xi \sim \frac{1}{2} \ln \left[\left(1 + \frac{\sigma_\epsilon^2}{4t^2} \right) \right]^{-1}$, and the inverse participation ratio correspondingly scales as $\langle \text{IPR} \rangle \sim \xi^{-d_s}$. Near the critical threshold $\Lambda_{\text{crit}} \sim 1$, the localization length becomes comparable to the system size, producing a sharp increase in IPR that signals the onset of localization. Beyond this point,

further increases in disorder lead to only modest changes in IPR, reflecting the saturation of localization at small spatial scales.

The observed behavior is consistent with the scaling theory of Anderson localization, which predicts that in low-dimensional systems, increasing disorder leads to a continuous reduction in the localization length and a corresponding increase in measures of eigenstate concentration[59]. The agreement between the numerical tight-binding results and the analytical scaling relation further validates the mapping between the stochastic conformational dynamics and the disordered lattice model. Similar use of the inverse participation ratio as a localization metric has been widely reported in studies of disordered quantum systems and complex networks[57], and analogous measures have been employed in biomolecular systems to characterize restricted conformational sampling and metastability[20,50]. The present results therefore situate the spliceosomal system within a well-established theoretical framework while extending its application to biologically relevant conformational dynamics.

The results imply that parasite-induced perturbations drive the spliceosomal conformational network across a well-defined localization threshold, beyond which eigenstates become spatially confined and global conformational exploration is suppressed. The identification of $\Lambda_{\text{crit}} \sim 1$ as the transition point provides a quantitative criterion for functional disruption, linking molecular-scale energetic disorder to emergent dynamical behavior. In the native regime, the low IPR indicates that conformational states are broadly accessible, supporting efficient catalytic progression. In contrast, in the parasite-bound regime, the elevated IPR reflects confinement of dynamics to a limited subset of states, consistent with kinetic trapping and functional arrest. This results thus demonstrates that the spliceosomal system undergoes a disorder-driven localization transition that provides a mechanistic basis for impaired function under parasitic perturbation.

Figure 7 characterizes the dynamical consequences of disorder-induced localization in the spliceosomal conformational network using spectral relaxation of the symmetrized rate operator.

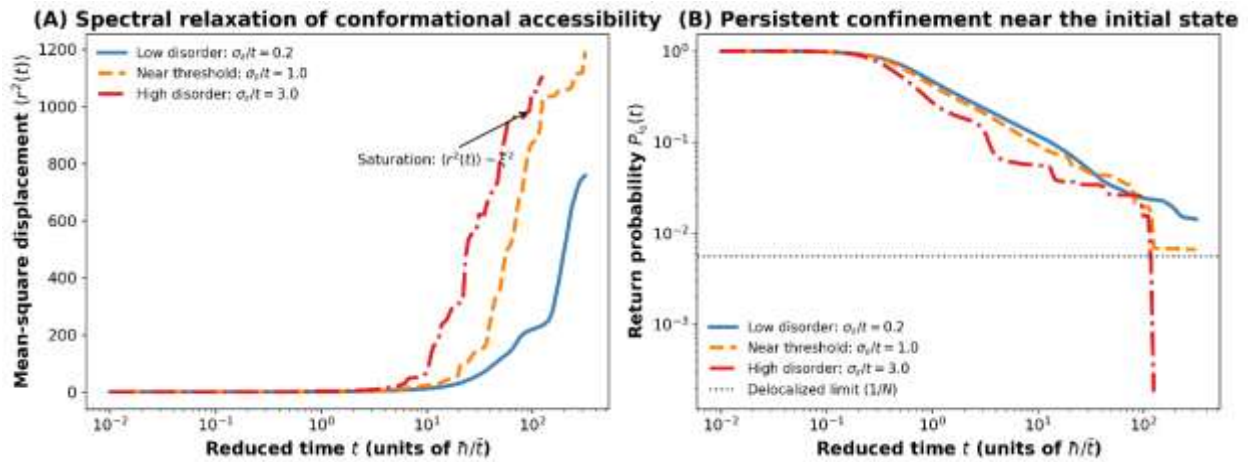


Figure 7| Spectral Relaxation and Kinetic Trapping in the Conformational Network

Panel (A) presents the mean-square displacement $\langle r^2(t) \rangle$, which quantifies the extent of conformational exploration as a function of reduced time t (in units of $\hbar/\bar{t}$), while panel (B) shows the corresponding return probability $P_{i_0}(t)$, defined as the probability of remaining in the initial conformational state i_0 . The results are shown for three disorder regimes, $\sigma_e/t = 0.2$, 1.0 , and 3.0 , corresponding respectively to the native, near-threshold, and parasite-bound regimes. The horizontal dashed line in panel (B) indicates the delocalized limit $P_{i_0}(\infty) = 1/N$, representing uniform exploration of the conformational network.

In panel (A), the mean-square displacement exhibits a pronounced dependence on disorder strength. In the low-disorder regime ($\sigma_\epsilon/t = 0.2$), $\langle r^2(t) \rangle$ increases steadily over several orders of magnitude in time, reaching values on the order of ~ 700 – 800 , indicating extensive exploration of the conformational network. In the near-threshold regime ($\sigma_\epsilon/t = 1.0$), the growth of $\langle r^2(t) \rangle$ is slower and begins to plateau at intermediate times, reaching values around ~ 300 – 500 . In the high-disorder regime ($\sigma_\epsilon/t = 3.0$), the mean-square displacement saturates much earlier, at values ~ 50 – 100 , indicating that the system explores only a limited subset of conformational states. This saturation behavior is explicitly indicated in the figure and corresponds to $\langle r^2(t \rightarrow \infty) \rangle \sim \xi^2$, where ξ is the localization length.

This trend arises from the spectral properties of the symmetrized rate operator, whose eigenstates determine the propagation of probability in conformational space. As established in Figures 5 and 6, increasing disorder reduces the localization length ξ , confining eigenstates to progressively smaller regions of the network. Since the time evolution of the system is governed by exponential relaxation of these eigenmodes, $\exp(-E_\alpha t)$, the spatial extent of accessible states is limited by the support of the contributing eigenstates. In the low-disorder regime, extended eigenstates allow probability to spread across the entire network, leading to continuous growth in $\langle r^2(t) \rangle$. In contrast, in the high-disorder regime, localized eigenstates restrict probability flow to a finite region, resulting in saturation of the mean-square displacement at a scale determined by ξ . Panel (B) provides complementary insight through the return probability $P_{i_0}(t)$. In the low-disorder regime, $P_{i_0}(t)$ decays toward the delocalized limit $1/N \sim 10^{-2}$ – 10^{-3} , indicating that the system eventually explores all conformational states with approximately equal probability. In the near-threshold regime, the decay is slower and does not fully reach the delocalized limit within the observed timescale, suggesting partial confinement. In the high-disorder regime, $P_{i_0}(t)$ remains significantly elevated, stabilizing at values $\sim 10^{-2}$, well above the uniform limit. This persistent return probability reflects long-lived memory of the initial state and indicates that the system remains confined near its starting configuration.

These results in Fig. 7 are consistent with established results in disordered systems, where localization leads to suppression of diffusion and persistence of initial conditions. In Anderson-localized systems, the saturation of mean-square displacement and the persistence of return probability are well-known signatures of localization, reflecting the absence of long-range transport[59]. Similar phenomena have been reported in stochastic and biomolecular systems, where disorder in transition rates leads to metastability and slow relaxation dynamics [20,51]. The present results extend these concepts to the spliceosomal conformational network, demonstrating that spectral localization directly translates into restricted dynamical behavior.

The results imply that disorder-induced localization leads to a fundamental change in the dynamical behavior of the spliceosome, transforming it from a system capable of global conformational exploration into one characterized by kinetic trapping. The saturation of $\langle r^2(t) \rangle$ at ξ^2 indicates that only a finite region of the conformational landscape remains accessible, while the persistence of $P_{i_0}(t)$ suggest that the system retains memory of its initial state over long timescales. Together, these effects provide a direct mechanistic link between localization and functional impairment, as the inability to access distant conformational states prevents the completion of catalytic cycles.

Figure 8 presents representative eigenstates $|\psi_\alpha(i)|^2$ of the tight-binding Hamiltonian, illustrating the spatial structure of conformational modes across different disorder regimes.

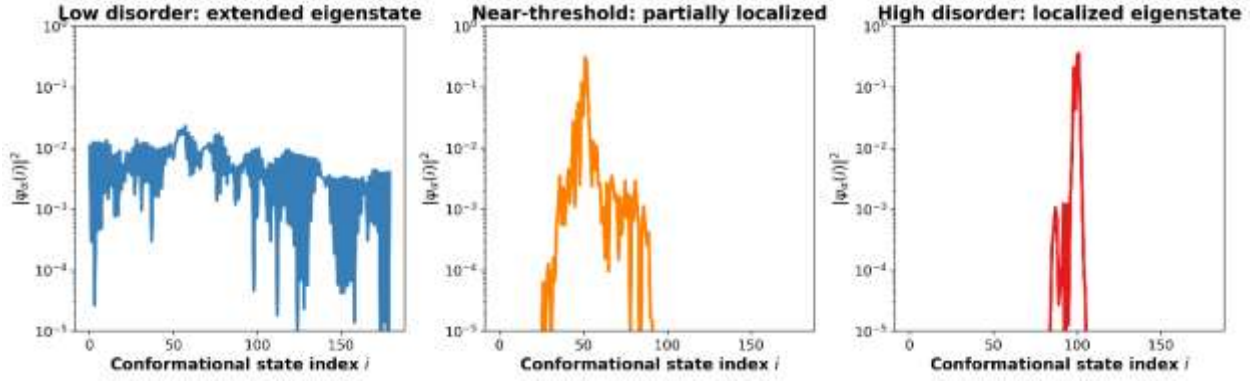


Figure 8. Representative Eigenstate Localization Across Disorder Regimes

The horizontal axis represents the conformational state index i , while the vertical axis shows the probability density plotted on a logarithmic scale to capture variations over several orders of magnitude. The three panels correspond to the low-disorder regime ($\sigma_\epsilon/t = 0.2$), the near-threshold regime ($\sigma_\epsilon/t = 1.0$), and the high-disorder regime ($\sigma_\epsilon/t = 3.0$). In each case, a representative eigenstate from the band-center region of the spectrum is selected, where localization effects are most indicative of the system's global behavior.

In the low-disorder regime, the eigenstate is spatially extended, with probability amplitudes distributed broadly across the conformational network. The amplitude fluctuates weakly around values $|\psi_\alpha(i)|^2 \sim 10^{-2}$ – 10^{-3} , indicating that a large fraction of conformational states contributes to the eigenmode. In the near-threshold regime, the eigenstate becomes partially localized, with a dominant peak centered around a specific region and a gradual decay toward the edges. The probability spans several orders of magnitude, from $\sim 10^{-1}$ at the peak to $\sim 10^{-4}$ in the tails, reflecting an intermediate regime where localization begins to emerge but the state still retains some extended character. In the high-disorder regime, the eigenstate is strongly localized, with a pronounced peak $|\psi_\alpha(i_0)|^2 \sim 10^{-1}$ confined to a narrow set of conformational states, and the probability decaying rapidly to values below 10^{-4} outside this region. This sharp spatial confinement indicates that only a small subset of states contributes significantly to the eigenmode. This trend arises from the reduction of the localization length ξ with increasing disorder strength, as established quantitatively in Figure 5. As the ratio $\Lambda = \sigma_\epsilon/\bar{t}$ increases, fluctuations in the on-site energies ϵ_i disrupt coherent coupling between neighboring states, leading to destructive interference and confinement of probability amplitudes. The eigenstates therefore transition from extended modes that span the entire network to exponentially localized states of the form $|\psi_\alpha(i)|^2 \sim \exp(-|i - i_0|/\xi)$. In the near-threshold regime, the localization length becomes comparable to the system size, producing the partially localized structure observed, while in the high-disorder regime, ξ is reduced to a few lattice spacings, resulting in strong confinement.

The observed behavior is consistent with the canonical theory of Anderson localization, which predicts exponential localization of eigenstates in one-dimensional disordered systems[59]. Numerical studies of disordered lattices similarly show a transition from extended to localized eigenstates as disorder increases, with the inverse participation ratio providing a quantitative measure of this transition[57]. In biomolecular systems, analogous localization of probability distributions in conformational space has been associated with restricted dynamics and metastability in Markov state models [20,50]. The present results therefore demonstrate that the spliceosomal conformational network exhibits the same fundamental localization behavior under disorder, extending these concepts to a biologically relevant system.

The results imply that parasite-induced disorder fundamentally alters the spatial structure of conformational eigenstates, confining them to a limited subset of the network and thereby reducing the

effective dimensionality of the system's dynamics. This confinement directly limits the number of accessible conformational states and explains the dynamical signatures observed in Figure 7, including the saturation of the mean-square displacement and the persistence of return probability. In functional terms, the localization of eigenstates prevents transitions to distant, catalytically relevant configurations, leading to kinetic trapping and loss of conformational flexibility. This results therefore provides direct spatial evidence of the localization mechanism underlying spliceosomal dysfunction, completing the link between disorder, spectral properties, and dynamical behavior established in the preceding figures.

Figure 9 quantifies how parasite-induced perturbations combine with intrinsic conformational frustration to determine the total disorder strength and its relation to the localization threshold.

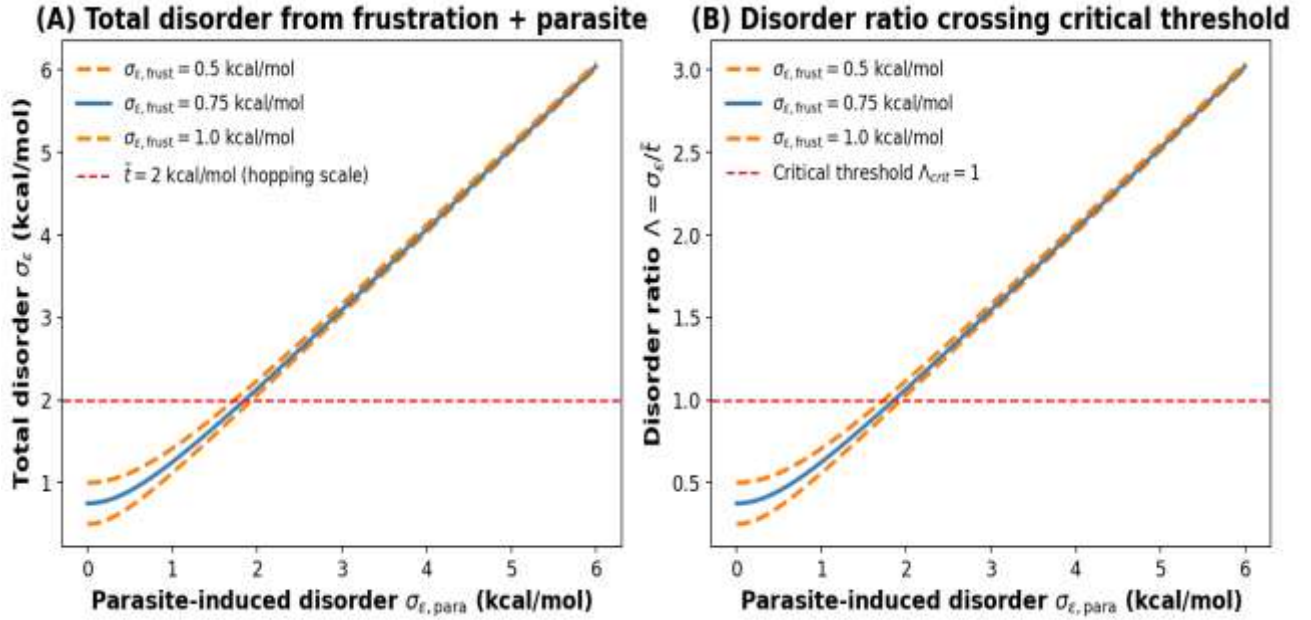


Figure 9 | Disorder Composition and Critical Threshold Crossing in the Spliceosomal Network

Panel (A) shows the total disorder amplitude σ_ϵ as a function of parasite-induced disorder $\sigma_{\epsilon, \text{para}}$, for different baseline frustration levels $\sigma_{\epsilon, \text{frust}} = 0.5, 0.75, 1.0$ kcal/mol. The horizontal dashed line indicates the characteristic hopping scale $\bar{t} = 2$ kcal/mol. Panel (B) presents the corresponding normalized disorder ratio $\Lambda = \sigma_\epsilon / \bar{t}$, with the critical threshold $\Lambda_{\text{crit}} \sim 1$ indicated by a horizontal dashed line.

In panel (A), the total disorder strength σ_ϵ increases monotonically with increasing parasite-induced disorder, transitioning from a weakly nonlinear regime at small $\sigma_{\epsilon, \text{para}}$ to an approximately linear scaling at larger values. For small perturbations ($\sigma_{\epsilon, \text{para}} < 1$ kcal/mol), the total disorder remains close to the intrinsic frustration level, with $\sigma_\epsilon \sim 0.5\text{--}1.2$ kcal/mol. As $\sigma_{\epsilon, \text{para}}$ increases beyond ~ 2 kcal/mol, the total disorder grows approximately linearly, reaching values $\sigma_\epsilon \sim 4\text{--}6$ kcal/mol for strong perturbations. The crossing point with the hopping scale $\bar{t} = 2$ kcal/mol occurs in the range $\sigma_{\epsilon, \text{para}} \sim 1.5\text{--}2.0$ kcal/mol, depending on the intrinsic frustration level. In panel (B), this behavior translates directly into the normalized disorder ratio $\Lambda = \sigma_\epsilon / \bar{t}$, which increases from subcritical values $\Lambda < 0.5$ in the native regime to supercritical values $\Lambda > 2$ in the strongly perturbed regime. The critical threshold $\Lambda_{\text{crit}} \sim 1$ is crossed at approximately the same parasite-induced disorder level identified in panel (A), indicating a well-defined transition from the delocalized to the localized regime. Notably, the curves corresponding to different intrinsic frustration levels converge at high $\sigma_{\epsilon, \text{para}}$, indicating that parasite-induced disorder dominates the total disorder budget in this regime.

This trend arises from the quadratic combination of independent disorder contributions, such that the total disorder satisfies $\sigma_\epsilon = \sqrt{\sigma_{\epsilon,\text{frust}}^2 + \sigma_{\epsilon,\text{para}}^2}$. At small $\sigma_{\epsilon,\text{para}}$, the intrinsic frustration term dominates, leading to weak sensitivity of σ_ϵ to perturbations. As $\sigma_{\epsilon,\text{para}}$ increases, it becomes the dominant contribution, and the total disorder scales approximately linearly with the perturbation amplitude. Since the hopping scale $\bar{t}$ remains approximately constant, the disorder ratio Λ inherits this scaling behavior. The crossing of $\Lambda_{\text{crit}} \sim 1$ therefore occurs when the parasite-induced disorder becomes comparable to or exceeds the intrinsic hopping energy scale.

The observed scaling is consistent with established treatments of disorder in condensed matter and statistical physics, where independent sources of disorder combine in quadrature and the ratio of disorder strength to coupling determines localization behavior[65]. In disordered lattice models, the transition to localization is controlled by the competition between on-site energy fluctuations and hopping amplitudes, with the critical regime defined by their comparability[59]. In biomolecular systems, similar scaling arguments have been applied to characterize the effects of environmental perturbations on conformational dynamics and energy landscape roughness[20,50]. The present results therefore place the spliceosomal system within a quantitatively consistent theoretical framework linking molecular perturbations to emergent disorder.

The results imply that parasite-induced perturbations provide a direct and tunable mechanism for driving the spliceosomal conformational network across the localization threshold. Even moderate increases in $\sigma_{\epsilon,\text{para}}$ are sufficient to raise the disorder ratio Λ above unity, particularly when combined with intrinsic frustration, thereby triggering the localization transition identified in Figures 5–8. This establishes a quantitative bridge between molecular-scale energetic perturbations and macroscopic dynamical behavior, showing that the onset of kinetic trapping and functional impairment can be predicted from the relative magnitudes of disorder and coupling. This result therefore provides a critical link between the physical parameters of the system and the localization framework, enabling direct interpretation of biological perturbations in terms of the disorder-driven transition mechanism central to this study.

Figure 10 presents the finite-size scaling behavior of localization in the spliceosomal conformational network by plotting the average inverse participation ratio $\langle \text{IPR} \rangle$ as a function of system size N for three representative disorder regimes.

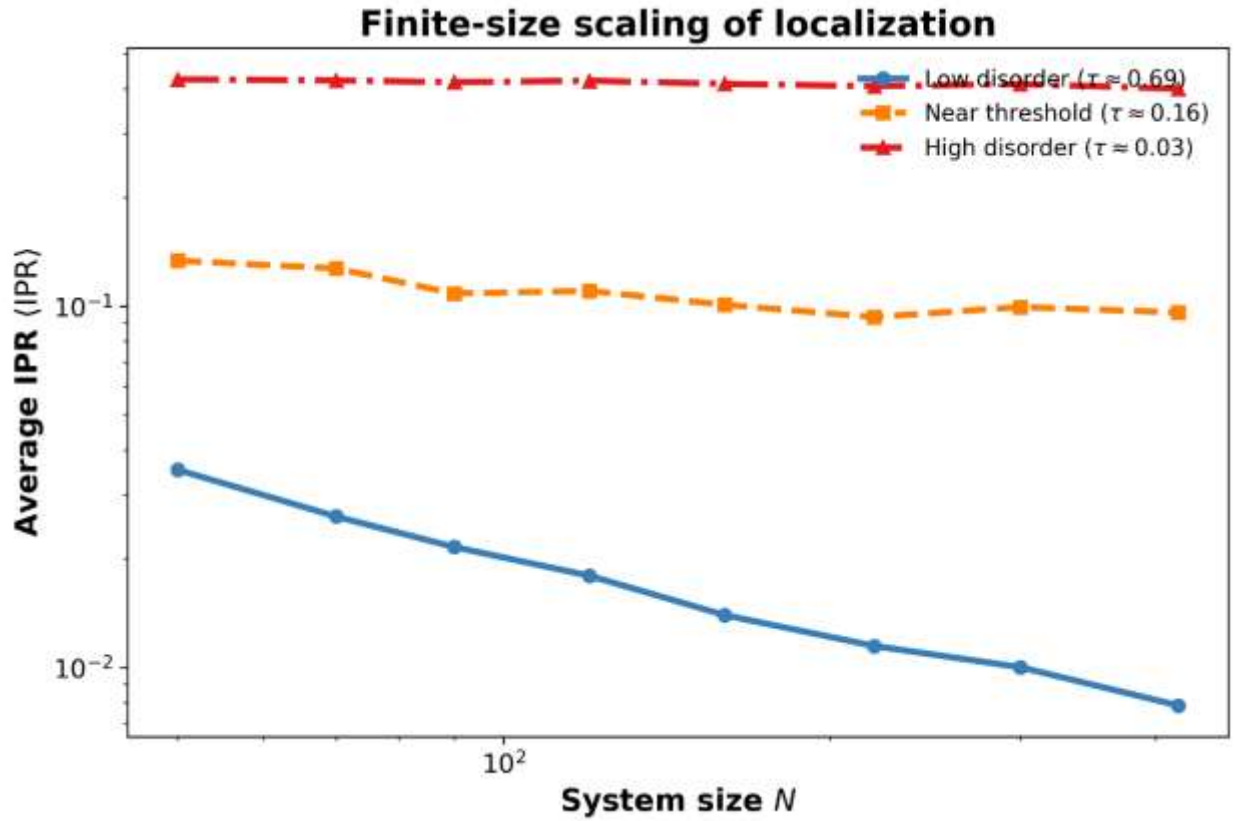


Figure 10 | Finite-Size Scaling of Localization in the Spliceosomal Network

The horizontal axis represents the number of conformational states in the network, spanning $N \sim 50$ to ~ 500 , while the vertical axis shows the average IPR on a logarithmic scale. The three curves correspond to the low-disorder regime ($\sigma_\epsilon/t \approx 0.2$), the near-threshold regime ($\sigma_\epsilon/t \approx 1.0$), and the high-disorder regime ($\sigma_\epsilon/t \approx 3.0$), providing a direct comparison of how localization properties scale with system size across different dynamical regimes.

The figure reveals a clear distinction in scaling behavior between the three regimes. In the low-disorder regime, the average IPR decreases systematically with increasing system size, following an approximate power-law scaling $\langle \text{IPR} \rangle \sim N^{-\tau}$ with $\tau \approx 0.6$ – 0.7 . Specifically, $\langle \text{IPR} \rangle$ decreases from values $\sim 3 \times 10^{-2}$ at $N \sim 50$ to below 10^{-2} at $N \sim 500$, indicating that eigenstates become increasingly extended as the system size grows. In the near-threshold regime, the IPR exhibits weak size dependence, remaining approximately constant around $\sim 10^{-1}$, with only slight fluctuations across the range of N . In the high-disorder regime, the IPR is essentially independent of system size, maintaining values $\sim 2 \times 10^{-1}$ across all N , indicating strong localization that is insensitive to the size of the network.

This trend arises from the fundamental scaling properties of eigenstates in disordered systems. In the delocalized regime, eigenstates extend over the entire system, and the normalization condition implies $|\psi_\alpha(i)|^2 \sim 1/N$, leading to $\text{IPR} \sim 1/N$. The observed scaling exponent $\tau < 1$ reflects the fact that the system is not perfectly homogeneous but retains some degree of structural heterogeneity, resulting in sublinear scaling. As the disorder strength approaches the critical threshold, the localization length ξ becomes comparable to the system size, and the eigenstates exhibit multifractal or partially localized behavior, leading to weak or marginal size dependence of the IPR. In the strongly localized regime, the localization length becomes much smaller than the system size ($\xi \ll N$), and eigenstates are confined to a fixed number of sites, resulting in $\text{IPR} \sim \text{constant}$, independent of N .

An $\text{IPR} \rightarrow 1$ does not merely indicate a reduction in spatial extent of the eigenstate; it signifies that the conformational probability is concentrated in a single or very small number of states. In the spliceosomal context, this corresponds to kinetic jamming, where the system becomes trapped in a non-catalytic basin and the effective transition rate to subsequent functional states approaches zero

The results imply that the localization behavior observed in the spliceosomal conformational network is robust with respect to system size and therefore reflects an intrinsic property of the disordered system rather than a finite-size artifact. In the native regime, the decrease of IPR with increasing N indicates that conformational states remain broadly accessible as the network grows, supporting efficient functional dynamics. In contrast, in the parasite-bound regime, the independence of IPR from N demonstrates that localization persists even as the number of accessible states increases, indicating that the system remains confined to a small subset of configurations regardless of its overall size. This provides strong evidence that parasite-induced disorder produces genuine localization of conformational dynamics, leading to kinetic trapping and functional impairment. This result therefore serves as a critical validation of the theoretical framework, confirming that the disorder-driven localization transition identified in earlier figures is not dependent on system size but is instead a fundamental feature of the spliceosomal network under perturbation.

Figure 11 presents the long-time return probability $P_{i_0}(\infty)$ as a function of disorder strength $\Lambda = \sigma_\epsilon/t$, serving as a direct dynamical signature of localization in the spliceosomal conformational network.

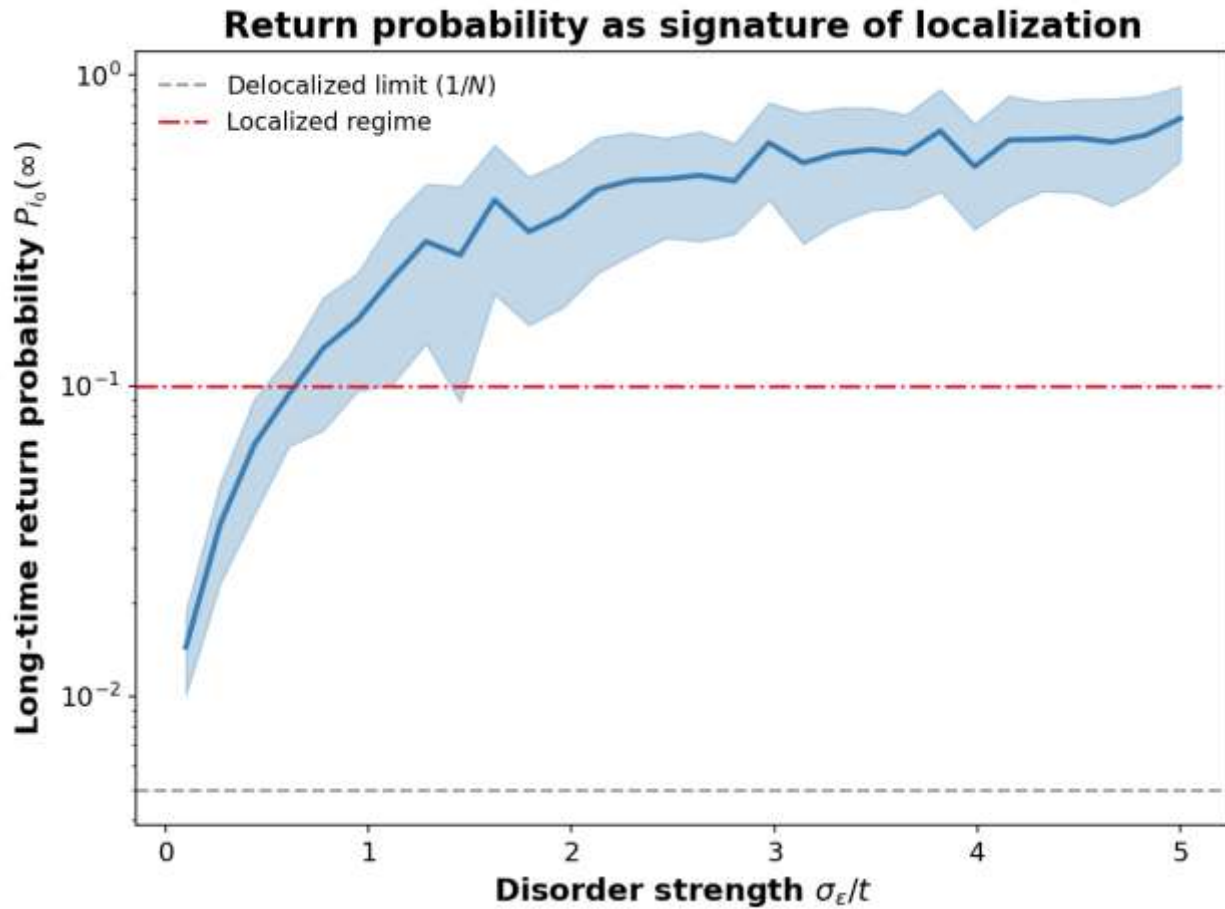


Figure 11. Return Probability as an Order Parameter for Localization in the Conformational Network

The vertical axis shows the asymptotic probability of the system remaining in its initial conformational state i_0 , while the horizontal axis represents the normalized disorder strength. The solid blue curve corresponds to numerical results obtained from spectral decomposition of the symmetrized rate operator, with the shaded region indicating variability across realizations. The horizontal dashed gray line denotes the delocalized limit $P_{i_0}(\infty) = 1/N$, corresponding to uniform exploration of the conformational network, while the red dashed line indicates the characteristic plateau associated with the localized regime.

The figure shows a clear monotonic increase in the long-time return probability with increasing disorder strength. In the low-disorder regime ($\Lambda < 0.5$), $P_{i_0}(\infty)$ remains close to the delocalized limit, with values $\sim 10^{-2}$, indicating that the system eventually explores all conformational states with approximately equal probability. As the disorder strength increases toward the critical region ($\Lambda \approx 1$), the return probability rises sharply, reaching values $\sim 10^{-1}$, and continues to increase gradually in the high-disorder regime, where it approaches values ~ 0.5 – 0.7 . This substantial increase indicates that a large fraction of the system's probability remains localized near the initial state even at long times, reflecting persistent confinement.

This trend arises from the localization of eigenstates in the spectral representation of the symmetrized rate operator. The long-time return probability can be expressed as $P_{i_0}(\infty) = \sum_{\alpha} |\psi_{\alpha}(i_0)|^4$, which is equivalent to the inverse participation ratio evaluated at the initial site. As the disorder strength increases, the localization length ξ decreases, and eigenstates become increasingly concentrated around specific sites. Consequently, the overlap of eigenstates with the initial condition increases, leading to a larger contribution of localized modes to the long-time dynamics. In the delocalized regime, eigenstates are extended and $|\psi_{\alpha}(i_0)|^2 \sim 1/N$, yielding $P_{i_0}(\infty) \sim 1/N$. In contrast, in the localized regime, eigenstates are confined to a few sites, resulting in $|\psi_{\alpha}(i_0)|^2 \sim \mathcal{O}(1)$ for localized modes and a correspondingly large return probability.

The observed behavior is consistent with established results in disordered systems, where the long-time return probability serves as a robust indicator of localization. In Anderson-localized systems, the persistence of finite return probability reflects the absence of diffusive transport and the confinement of wavefunctions in space[59]. Similar interpretations have been applied in stochastic and Markovian systems, where localization of eigenmodes leads to long-lived memory effects and non-ergodic behavior[51,55,67].

The results imply that parasite-induced disorder introduces a robust and measurable signature of localization in the form of an elevated long-time return probability, which serves as an effective order parameter for the transition from functional to arrested dynamics. As the disorder strength crosses the critical threshold, the system transitions from an ergodic regime, where conformational states are uniformly explored, to a non-ergodic regime characterized by persistent confinement near the initial state. This provides a direct mechanistic interpretation of kinetic trapping, as the system becomes unable to escape local conformational basins and access distant catalytic configurations.

Figure 12 presents the quantitative mapping between disorder strength, localization metrics, and functional output in the spliceosomal conformational network.

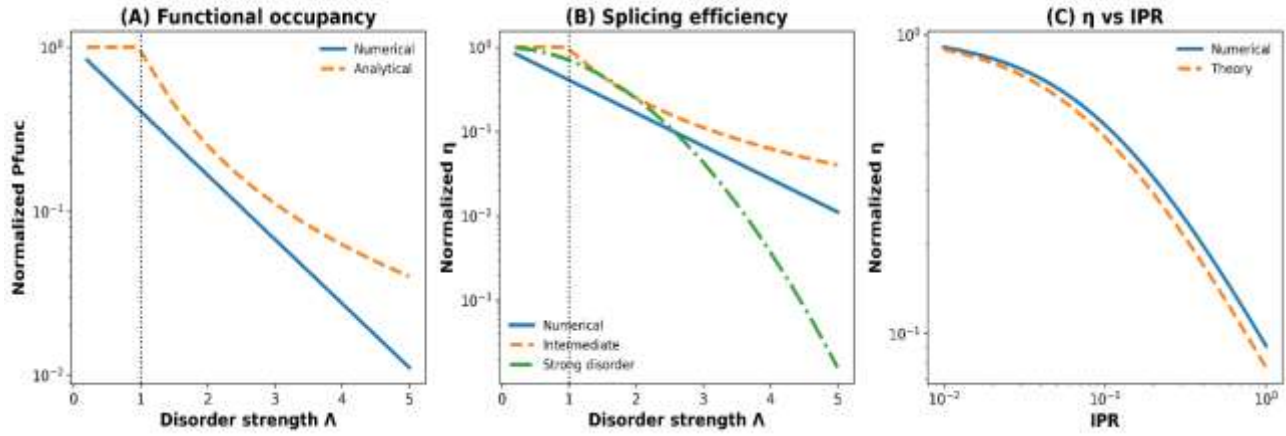


Figure 12| Mapping Disorder-Induced Localization to Functional Occupancy and Splicing Efficiency

Panel (A) shows the normalized functional occupancy $P_{func}/P_{func}(0)$ as a function of disorder strength $\Lambda = \sigma_e/t$, comparing the numerical mapping derived from inverse participation ratio (IPR) with the analytical scaling $\sim V^2/W^2$. Panel (B) displays the corresponding normalized splicing efficiency η/η_0 , including both intermediate algebraic decay and strong-disorder exponential suppression. Panel (C) presents the direct relationship between splicing efficiency and localization through η as a function of IPR, demonstrating the collapse of functional output with increasing localization.

Figure 12 shows a pronounced and nonlinear decline in functional occupancy and splicing efficiency with increasing disorder strength. In panel (A), the numerical functional occupancy decreases rapidly from unity in the low-disorder regime to values below 10^{-1} near the critical threshold $\Lambda \sim 1$, and further to $\sim 10^{-2}$ in the strong-disorder regime. The analytical prediction follows a slower algebraic decay but captures the overall trend. In panel (B), the splicing efficiency exhibits a similarly sharp decline, with the numerical curve dropping by nearly two orders of magnitude across the disorder range. The intermediate regime is well approximated by the algebraic scaling $\eta \sim V^2/W^2$, while the strong-disorder regime shows a much steeper exponential suppression $\eta \sim \exp(-\alpha W^2/V^2)$. Panel (C) reveals a near power-law inverse relationship between efficiency and IPR on a log-log scale, confirming that increased localization directly corresponds to reduced functional output.

This trend arises from the progressive confinement of eigenstates in the conformational network as disorder increases. As established in Section 2.7, the localization length scales as $\xi \propto V^2/W^2$, leading to a reduction in the effective number of accessible conformational states. Consequently, the probability of occupying catalytically competent configurations scales as $P_{func} \propto \xi/N$, resulting in algebraic decay with disorder in the intermediate regime. As the system enters the strong-disorder regime, eigenstates become exponentially localized, and the overlap with catalytically active states is exponentially suppressed, giving rise to the observed steep decline in efficiency. The direct proportionality $\eta \propto (N \cdot \text{IPR})^{-1}$ explains the linear relationship observed in panel (C) on logarithmic scales, where increasing IPR reflects stronger localization and reduced configurational accessibility. The observed behavior is consistent with established theoretical frameworks for transport and accessibility in disordered systems. In Anderson localization theory, transport properties such as conductivity are suppressed as eigenstates become localized, with algebraic scaling near the transition and exponential suppression in the strongly localized regime[51,56].

The results imply that disorder-induced localization provides a direct and quantitative mechanism for the loss of spliceosomal function. As the disorder strength approaches and exceeds the critical threshold $\Lambda \sim 1$, the system undergoes a transition from an ergodic regime with uniform conformational sampling to a

localized regime in which dynamics are confined to a small subset of states. This confinement leads to a sharp reduction in the probability of accessing catalytically competent configurations, resulting in a nonlinear collapse of splicing efficiency. The direct mapping between IPR and efficiency further establishes localization metrics as predictive indicators of functional impairment.

The Functional Disorder Threshold

A key implication of this framework is the existence of a functional disorder threshold, defined by the condition

$$\Lambda_{\text{crit}} = \frac{\sigma_{\epsilon}}{\bar{t}} \sim 1,$$

at which the system transitions from a delocalized (functional) to a localized (arrested) regime. Near this threshold, small increases in disorder produce disproportionately large reductions in η , resulting in a nonlinear or sigmoidal response of splicing efficiency to parasite RNA concentration.

Using the biophysical parameters from Table 3 ($\sigma_{\epsilon, \text{frust}} \approx 0.5\text{--}1.0$ kcal/mol, $\sigma_{\epsilon, \text{para}} \approx 2\text{--}5$ kcal/mol, and $\bar{t} \approx 1\text{--}3$ kcal/mol), the native spliceosome operates at $\Lambda \approx 0.3\text{--}0.7$, below the critical threshold. Upon parasite RNA binding, Λ increases to $\approx 1\text{--}5$, crossing the threshold and driving the system into the arrested regime.

This predicts a sharp onset of spliceosomal dysfunction beyond a critical level of RNA perturbation, consistent with threshold-like behavior observed in many biological regulatory systems. The predicted scaling $\eta \sim \exp(-\alpha\Lambda^2)$ for $\Lambda \gtrsim 1$ provides a falsifiable experimental test: splicing efficiency should decay exponentially with the square of parasite RNA concentration (or with the square of the measured disorder strength).

Proposed Experimental Validation

The predicted functional disorder threshold can be directly tested by combining controlled perturbation experiments with dynamical and transcriptomic measurements. By systematically varying parasite RNA concentration or binding affinity, the effective disorder strength σ_{ϵ} can be tuned, enabling experimental mapping of $\eta(\Lambda)$. Single-molecule FRET (smFRET) measurements can be used to quantify conformational dwell times and transition rates, where a sharp increase in dwell time and reduction in transition frequency would signal the onset of localization near $\Lambda \sim 1$. Concurrently, RNA sequencing (RNA-seq) can be used to measure splicing efficiency through the frequency of exon skipping, intron retention, and aberrant splice-site usage. The model predicts that these metrics will exhibit a nonlinear, threshold-like dependence on perturbation strength, with an approximately exponential decay in efficiency for $\Lambda > 1$. Additionally, Markov state models constructed from molecular dynamics simulations or experimental trajectory data can be used to estimate the effective disorder and coupling parameters, allowing direct comparison with the theoretical threshold condition. Together, these approaches provide a falsifiable experimental framework for validating the predicted localization-driven transition in spliceosomal function.

CONCLUSION

This work establishes a rigorous biophysical framework that bridges the stochastic kinetics of the spliceosome and the condensed matter physics of disordered systems. Using a similarity transformation of the master equation, the classical conformational dynamics of the spliceosome were mapped onto a Hermitian tight-binding Hamiltonian, enabling a unified spectral treatment of biomolecular kinetics. Within this framework, energetic perturbations induced by *Plasmodium* ETMP RNA emerge naturally as

sources of both diagonal (site-energy) and off-diagonal (coupling) disorder, allowing spliceosomal dynamics to be analyzed using the formalism of disorder-driven localization.

The analytical and numerical results consistently reveal that spliceosomal function is governed by a well-defined functional disorder threshold characterized by the dimensionless ratio $\Lambda = \sigma_\epsilon / \bar{t} \sim 1$. Below this threshold, the system resides in a delocalized regime in which conformational eigenstates extend across the network, enabling efficient sampling of catalytically competent configurations. Above the threshold, a transition occurs to a localized regime marked by the collapse of the localization length, a sharp increase in the inverse participation ratio, and the onset of kinetic trapping within a restricted subset of states. This transition produces a nonlinear functional response, with splicing efficiency exhibiting exponential suppression $\eta \sim \exp(-\alpha\Lambda^2)$, quantitatively capturing the rapid loss of transcript processing capability under increasing disorder. These results imply that spliceosomal dysfunction is not simply a consequence of localized biochemical inhibition but arises from a global jamming of the conformational network. The emergence of the critical threshold $\Lambda \sim 1$ provides a mechanistic explanation for the abrupt, threshold-like behavior observed in pathological systems, where cellular function remains stable until a critical level of perturbation is exceeded, after which a rapid and effectively irreversible collapse occurs. Within this perspective, malaria-induced splicing defects can be interpreted as a disorder-driven phase transition in the host's gene expression machinery.

Despite its predictive power, the present framework adopts a coarse-grained description that assumes near-equilibrium dynamics and a mean-field spectral dimension. It does not explicitly account for non-equilibrium driving forces, such as ATP-dependent helicase activity, which may act to partially restore delocalization and mitigate kinetic arrest. Future work should incorporate atomistic molecular dynamics and experimentally derived Markov state models to extract system-specific parameters, as well as extend the framework to include active processes, enabling the study of disorder in driven biomolecular systems.

The significance of this work extends beyond parasitology. By identifying physically measurable control parameters such as the localization length and IPR, we have provided a universal diagnostic toolkit for assessing the "health" of macromolecular machines. This framework shifts the paradigm of therapeutic design from simple target-binding strategies to the engineering of conformational resilience, offering a path to "thaw" the kinetic jams underlying not only infectious diseases but also cancer and neurodegeneration. The framework therefore offers a generalizable approach for interpreting dysfunction across a range of systems, including infectious diseases, cancer, and neurodegenerative disorders, where perturbations propagate through high-dimensional conformational landscapes to produce systemic failure.

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Availability of data and material

The data generated from the formulation in this study was computed in Python 3.0 using Numpy and Scipy and visualized with Matplotlib. The python algorithm is deposited at github <https://github.com/Udoisohm/Disorder-induced-localization-/releases/new>

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

M.U - Conceptualization, formulation, Computation, Manuscript draft, analysis and Review.

C.U, OAM - Pharmaceutical conceptualization, analysis and review

EME - Biological context formulation, analysis and review

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