Supporting Information

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SI Text

Stochastic Resonance (SR) in the Presence of Handles. To study whether the SR is still realized when the weak signal is indirectly exerted to the system through handle polymers, just like in the real experimental condition in laser optical tweezers (LOTs), we simulate folding dynamics of an RNA hairpin by attaching stiff handles to the two of the P5GA RNA hairpin modeled with SOP representation (Eq. **2** in the main text). Each handle is modeled by using the following energy potential (1):

$$H_{\text{handles}} = \frac{k_S}{2}\sum_{i=1}^{N-1}(r_{i,i+1} - r_0)^2 - k_A\sum_{i=1}^{N-2}\hat{r}_{i,i+1}\cdot\hat{r}_{i+1,i+2}. \qquad \textbf{[S1]}$$

The first term denotes the chain connectivity, with an equilibrium distance $r_0 = 0.5$ nm and spring constant $k_S = 1.4\times 10^4$ pN $\cdot$ nm^{-1}. The second term is the bending penalty potential with bending modulus $k_A = 561$ pN $\cdot$ nm, which gives rise to the persistence length $l_p = 70$ nm. We take $N = 40$ for the length of handle, which amounts to the contour length of $L = 20$ nm. Fig. S1 shows time trajectories of the extension of the entire system, which includes the extension of two handles, at $f = 17$ pN and $\delta f = 1.4$ pN, for three different driving periods. The molecular extension $z(t)$ (left) and the total extension $z_L(t)$ (right) are depicted in the red and black axes, respectively. As shown in the trajectories, the phase of $z_L(t)$ is compatible with that of $z(t)$. Even in the presence of handles, the SR is realized at an optimal period 60 ms (Fig. S1*B*) where the folding transitions are synchronized to the frequency of external driving. The other trajectories under relatively fast (Fig. S1*A*) and slow (Fig. S1*C*) driving show random transitions regardless of the drivings. As is discussed in the main text and in the ref. 1, the presence of the handles pins the overall molecular motion and slows down the transition kinetics of the molecule sandwiched between the handles. We have estimated that the transition dynamics with handles with $l_p = 70$ nm and $L = 20$ nm tend to be almost about sixfold slower (1) than the Kramers times (≈10 ms for folding and ≈0.7 ms for unfolding) without handles, which we have considered in the text, and found SR (Fig. S1*B*) at an optimal driving period $T_\Omega \approx 60$ ms, which is approximately sum of the Kramers times.

SR at the Transition Midforce. To demonstrate the SR using LOTs experiment, it would be most straightforward to perform the experiment around the external force value near the transition midforce, at which the transition from one basin to another is most frequent. To show SR under the transition midforce ($f_m = 14.7$ pN), we have performed the SOP simulations for hopping (folding and unfolding) dynamics of a P5GA under f_m. Fig. S2 shows time trajectories of the P5GA extension $z(t)$ for three different driving periods, at $\delta f = 1.4$ pN. SR is clearly shown in the Fig. S2*B* at an optimal driving period $T_\Omega = 4$ ms. In this case, the optimal driving period is found to be around twice the mean hopping transition time ($\approx 2\tau_F(f = f_m) \approx 4$ ms; see also Fig. 1*C* where $\tau_F = \tau_U = 2$ ms), in consistent with the time-scale matching condition as has extensively been discussed in the SR community (2–4). The other trajectories, under relatively faster (Fig. S2*A*) and slower (Fig. S2*C*) drivings that deviate from the optimal frequency, show random transitions.

1. Hyeon C, Morrison G, Thirumalai, D (2008) Force dependent hopping rates of RNA hairpins can be estimated from accurate measurement of the folding landscapes. *Proc Natl Acad Sci USA*, 105:9604–9606.
2. Gammaitoni L, Hänggi P, Jung P, Marchesoni, F (1998) Stochastic resonance. *Rev Mod Phys*, 70:223–287.
3. Schmitt C, Dybiec B, Hänggi P, Bechinger C (2006) Stochastic resonance vs. resonant activation. *Europhys Lett*, 74:937–943.
4. Gammaitoni L, Marchesoni F, Dantucci S (1995) Stochastic resonance as a bona fide resonance. *Phys Rev Lett*, 74:1052–1055.

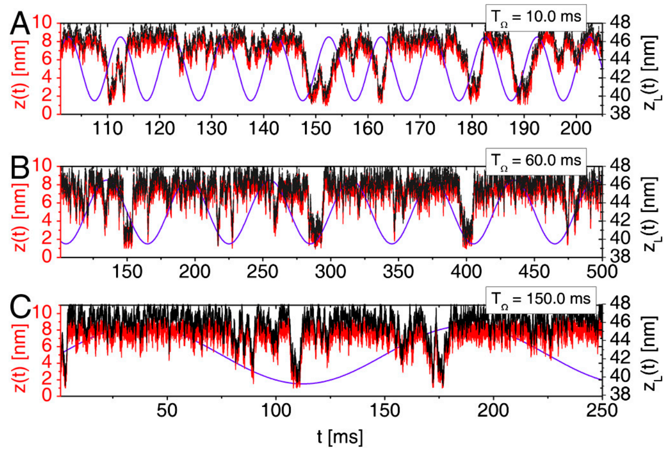

Fig. S1. Demonstration of RNA hairpin trajectories under SR condition in the presence of handles. Together with the SOP representation of RNA hairpin, we considered the handle of contour length $L = 20$ nm and persistence length $l_p = 70$ nm. The time trajectories of molecular extension $z(t)$ (red; left axis) and the extension with handles $z_L(t)$ (black; right axis) are displayed at constant tension $f = 17$ pN, driving force $\delta f \sin(\Omega t)$ with $\delta f = 1.4$ pN, and period $T_\Omega = 2\pi/\Omega$. The phase of extensions $z_L(t)$ overlaid on the $z(t)$ is in good agreement. Both $z(t)$ and $z_L(t)$ show random transitions at (*A*) $T_\Omega = 10.0$ ms and (*C*) $T_\Omega = 150.0$ ms. (*B*) The folding transitions are synchronized with an optimal driving period $T_\Omega = 60.0$ ms. The blue curves are overlaid to show the phase of oscillatory driving forces.

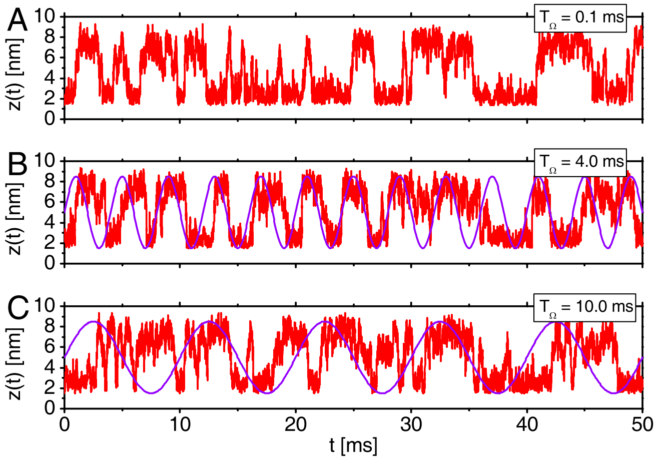

Fig. S2. Demonstration of bona-fide SR using the SOP model under the transition midforce $f_m = 14.7$ pN in the absence of handles. We depicted time trajectories of molecular extension $z(t)$ at f_m and $\delta f \sin(\Omega t)$ with $\delta f = 1.4$ pN and period $T_\Omega = 2\pi/\Omega$. $z(t)$ show random transitions at (*A*) $T_\Omega = 0.1$ ms and (*C*) $T_\Omega = 10.0$ ms, while coherent transitions occur at an optimal period (*B*) $T_\Omega = 4.0$ ms. The blue curves are overlaid to show the phase of oscillatory driving forces.