## SUPPLEMENTARY INFORMATION

## Influence of ionic strength on persistence length and knotting probability

In our simulations, we have assumed a persistence length of 50 nm over the entire range of ionic conditions. However, experimental studies (Sobel and Harpst, 1991; Kam et al., 1981; Manning, 1981; Post, 1983), computer simulations (Rieger and Virnau, 2018; Savelyev, 2012) and theoretical works (Manning, 2006) indicate that for short strands (in the kilo base regime) persistence length decreases considerably (to about 30 to 35 nm) in high salt conditions and also depends somewhat on the actual ions used in the buffer.

In this section, we argue that our simplified approach is nevertheless justified at least with respect to knotting probabilities. Note, that in terms of our coarse-grained model, a reduction of persistence length effectively corresponds to a decrease in stiffness according to equation 2 from the main text. To test this effect, we have rescaled our simulations for physiological conditions ( $\kappa = 11.673$  and d = 4.465 nm corresponding to  $l_p = 50$  nm) to 1M ( $\kappa = 11.673$  and d = 2.95 nm corresponding to  $l_p = 34.4$  nm, compare with eq. 2 ) and compared those results with our simulations for 1M assuming a persistence length  $l_p = 50$  nm (at  $\kappa = 16.949$  and d = 2.95 nm). As shown in Fig. 1 knotting probabilities are only affected marginally as they depend little on stiffness in this regime as already noted, e.g., by Virnau et. al. in (Virnau et al., 2013).



**Figure 1.** Percentage of knotted strands as a function of DNA length at 1M salt concentration assuming a persistence length  $l_p$  of 50 or 35 nm.

Furthermore, Brunet et. al (Brunet et al., 2015)) showed that in high salt conditions persistence length also increases with DNA length, so the effective persistence length might actually be closer to 50 nm for strand sizes considered in our study. This, together with the fact that knotting probability only changes little with stiffness for large values of  $\kappa$  (Fig. 1) justifies our simplified assumption.

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