Orientation of DNA minicircles balances density and topological complexity in kinetoplast DNA

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Abstract

Kinetoplast DNA (kDNA), an essential mitochondrial structure common to trypanosomes and *Leishmania*, contains thousands of DNA minicircles that are densely packed and topologically linked into a chain mail-like network. Experimental data indicate that every minicircle in the network is, on average, singly linked to three other minicircles (i.e., has mean valence 3) before replication and to six minicircles in the late stages of replication. The biophysical factors that determine the topology of the network and its changes during the cell cycle remain unknown. Using a mathematical modeling approach, we previously showed that volume confinement alone can drive the formation of the network and that it induces a linear relationship between mean valence and minicircle density. Our modeling also predicted a minicircle valence two orders of magnitude greater than that observed in kDNA. To determine the factors that contribute to this discrepancy we systematically analyzed the relationship between the topological properties of the network (i.e., minicircle density and mean valence) and its biophysical properties such as DNA bending, electrostatic repulsion, and minicircle relative position and orientation. Significantly, our results showed that most of the discrepancy between the theoretical and experimental observations can be accounted for by the orientation of the minicircles with volume exclusion due to electrostatic interactions and DNA bending playing smaller roles. Our results are in agreement with the three dimensional kDNA organization model, initially proposed by Delain and Riou, in which minicircles are oriented almost perpendicular to the horizontal plane of the kDNA disk. We suggest that while minicircle confinement drives the formation of kDNA networks, it is minicircle orientation that regulates the topological complexity of the network.

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