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## The soft breeze of the cation atmosphere around DNA

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Ions are indispensable to living organisms: in addition to their central role in, *e.g.* conveying neural signals and maintaining homeostasis via osmosis, they also have a strong impact on the structure of biological macromolecules. Remarkably, this structural effect can radically change with the nature of the ion. The importance of the ion's nature on the interaction with proteins was already recognized in a pioneering work by Hofmeister "On the Doctrine of the Action of Salts" published back in 1888. In this study, the abilities of different salts to precipitate globulin in egg white (1) were carefully quantified, leading to the well-known Hofmeister series. While a molecular interpretation of ion-specific interactions with proteins was recently proposed (2), a comparable understanding of ion-nucleic acid interactions is still missing. A unique feature of DNA and RNA lies in the tremendous negative charge due to the phosphate backbone. This charge is neutralized by the presence of many cationic counterions around the nucleic acid, forming what is commonly called the ion atmosphere. However, due to its diffuse character, this ion atmosphere is very difficult to characterize structurally and only a small proportion of cations can be resolved in X-ray crystallography. Typical categories such as "tightly bound site," first or second coordination layers cannot be defined straightforwardly. In addition, DNA is a peculiar polyelectrolyte and the dynamics of cations in the DNA ion atmosphere is poorly known. Indeed, residence times of most cations bound to DNA are short (nanosecond and shorter). Theoretically understanding this ion atmosphere is also far from trivial. Both simple condensation models (3), or full Poisson-Boltzmann theory fail to grasp the molecular details of cation-DNA interactions (4).

The study of Iwahara and coworkers that appears in this issue is therefore a very timely and welcome contribution to advance our understanding of the DNA ion atmosphere. The authors contrast the DNA ion atmosphere dynamics of several monovalent ions with different sizes and solvation spheres, which span the Hofmeister series (5). They record and compile data for four ions with different sizes and solvation spheres. They elegantly use simple lithium-7 and cesium-133 NMR methods to measure how translational diffusion of ions is perturbed by the presence of DNA. Translational diffusion is characterized on timescales of the order of 10 ms and over length scales of a few micrometers. The timescales are orders of magnitude longer than the residence time of ions in the atmosphere, which is estimated to *ca.* 1 ns by the authors, and the length scales are much longer than the dimensions of the investigated DNA duplex. Under these conditions, the diffusion coefficients are the weighted averages of the diffusion coefficients in the atmosphere and in the bulk. Disentangling both quantities was obtained from titrations with DNA. Iwahara and coworkers find that the diffusion coefficients of the cations are reduced by about 40% in the atmosphere. But the most striking result is that in spite of the very different ionic sizes and solvation properties, the reduction of diffusion coefficients relative to the bulk is the same for all investigated ions, including Li<sup>+</sup>, Na<sup>+</sup>, NH<sub>4</sub><sup>+</sup>,

and Cs<sup>+</sup>. This result is unexpected and very informative. For instance, if diffusion in the ion atmosphere was limited by site-interactions at the surface of DNA, the slowdown induced by DNA would be ion specific and large variations would be expected for this series of cations. The authors choose to describe the dynamics of cations in the atmosphere as diffusion on a rough surface of potential, which is not only a relevant description but also appropriate given the scarce information at hand: a diffusion coefficient averaged over all states in the atmosphere.

The results by Iwahara and coworkers will assuredly stimulate further experimental and theoretical studies to elucidate the molecular factors that explain the uniform slowdown in cation diffusion caused by DNA, and to characterize the interactions between DNA and its ion atmosphere. The importance of the shape of the DNA solute should be investigated, and temperature-dependent studies could, for example, be instructive to examine the entropic nature of this effect. One may also speculate that this uniform slowdown affecting all cations might be mediated by water and arise from an effect of DNA on the surrounding hydration layers, whose slower dynamics would impede the cation dynamics; the similarity between the slowdown found here for cations by Iwahara and that determined for the DNA hydration shell dynamics in prior studies (6) suggests that this effect would be worth exploring. One can certainly trust that the combination of experiments like the one reported here by Iwahara and coworkers with molecular dynamics simulations should soon offer answers to these questions and provide a better understanding of electrostatic interactions that are essential for the stability and molecular properties of DNA.

#### **Declaration of interests**

The authors declare no competing interests.

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