Again about Schrödinger's 'aperiodic crystal'

1. **Properties of Rouse polymers with actively driven regions**
   Authors: Dino Osmanović
   J Chen Phys, v. **149**, 164911 (2018)

2. **Delayed Excitations Induce Polymer Looping and Coherent Motion**
   Authors: Andriy Goychuk, Deepti Kannan, and Mehran Kardar
   Phys Rev Lett, v. **133**, 078101 (2024)

3. **Role of Charge Sequence in Polyampholyte Aggregation**
   Authors: Nam-Kyung Lee, Seowon Kim, Youngkyun Jung, and Albert Johner
   Macromolecules, v. **57**, 7474-7488 (2024)

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Erwin Schrödinger famously coined an intentionally paradoxical term 'aperiodic crystal', to describe what we now know to be the sequences of diverse monomer units in biological polymers of DNA, RNA, and proteins [1]. These sequences are genetically controlled, and thus 'aperiodic', but typically do not change in thermal motion or usual dynamics of biopolymers, akin to a 'crystal'. In more recent times, particularly in the context of protein folding studies, a lot of attention was attracted to the idea that these sequences are deeply similar to specific realizations of quenched disorder (see the list of references in the review [2]). Thus, the problem of heteropolymers with quenched sequences is by no means new, it keeps reappearing in a variety of fields - and, I think, still awaits deeper insights. Here, I want to attract attention to the two entirely unrelated papers – both of which, however, deal with this very problem, albeit in very different contexts.

Dino Osmanović in the first recommended paper considers the dynamics of a polymer chain in which some monomers are 'active', while others are 'passive'. That means, passive monomers are driven by the regular thermal delta-correlated Langevin noise, while active monomers are subjected to random non-thermal forces, with amplitudes unrelated to thermal energy and possibly with some non-zero correlation time. The main motivation for this model is chromatin – a functional form of DNA in a cell. In every particular cell, some part of chromatin (called euchromatin) involves genes that are actively transcribed and thus interact with energy consuming (ATP dependent) working enzymes, such as RNA polymerase, while other parts of chromatin (called heterochromatin) are passive. For the reasons that are

not understood and intensively debated in the literature, euchromatin and heterochromatin tend to have different densities and tend to belong to different spatial domains. Osmanović model is intended as a step to addressing this puzzle. The fact that the model is based on Rouse polymer dynamics (i.e., neglects hydrodynamics of the nucleoplasm) and also neglects excluded volume interactions is solely justified by the simplicity considerations. As far as the sequence problem is concerned, the author assumes the sequence to be periodic – which is yet another simplicity assumption, allowing a complete (and elegant) analytical solution. In a more recent study [3], authors undertake a large scale molecular dynamics simulation, which allows them to fully account for the excluded volume constraints (albeit not hydrodynamics) – but as far as the sequences are concerned, they are still at the same level, considering only the periodic sequences (specifically, the sequences of blocks). The same is true for the paper [4], where driving active force is assumed delta-correlated in time, but correlated between monomers along the chain; authors perform simulations based on actual HiC data, but as far as analytically considered example – it is still periodic in terms of the underlying sequence.

A new spin on these developments is added by the second recommended paper, that by Andriy Goychuk, Deepti Kannan, and Mehran Kardar. These authors still consider a Rouse polymer with no hydrodynamic interactions, but take a more general model of active driving excitations that are correlated both in time and along the chain. They show that driving different monomers at different times generates the possibility of spatial correlations between distant monomers that are programmed not by the physical interactions of monomers, like in old-fashioned models of protein folding, but by the time delays. I don't think it resolves the puzzle of how to understand the sequence-imposed complexity, but definitely adds a new flavor to it.

In general, it is not clear to me to what extent the insights gained from the periodic sequence model are instructive if we really want to think about chromatin (which, needless saying, is not periodic at all).

The third of the recommended papers, by Nam-Kyung Lee et al, treats a very different subject. While Osmanović studies an active energy consuming and very non-equilibrium system, Lee et al examine a purely equilibrium mixture of polymer chains with both positively and negatively charged monomers – called polyampholytes. As we know from Debye and Hückel theory (which is 101 years old this year [5]), mobile positive and negative ions, if present in equal numbers, position themselves in a correlated non-random way, such that the corresponding correlation energy is negative (favorable). When these ions are connected to long chains, their ability to choose favorable spatial arrangement is frustrated by the chain. Nevertheless, overall neutral polyampholyte chains (or overall neutral groups of such chains) are known to shrink, form globules, or sediment, similar to the complexes of oppositely charged polyelectrolytes [6]. Early cavalier treatments simply assumed that frustrations imposed for a polyampholyte by the chain connectivity can be neglected [7]. This is probably true for overall neutral and sufficiently uniform sequences of pluses and minuses. Of course, if the system is not neutral and one of the charge signs strongly overwhelms the other, then electrostatic repulsion dominates. An open question, where sequence of pluses and minuses sensitively comes into play, arises for an intermediate case, when chain or complex is not fully neutral, but prevalence of one charge sign over the other is marginal. Nam-Kyung Lee et al study this problem by means of molecular dynamics simulation and come to the conclusion that the so-called 'blockiness' of the sequence is the determining property of the system.

Although authors did not seem to place much emphasis on that, it seems that in this case periodic sequences might lead to peculiar, perhaps periodic, spatial structures (microphase separation, or crystals).

In summary, the three recommended papers may not be closely related, but I think their juxtaposition highlights the fact that quenched aperiodic sequences of biopolymers – indeed, the aperiodic crystals – still await a penetrating physics insight.

References

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