



OPEN Molecular simulation study of RNA/dopamine complex dynamics at varying concentrations

Armen H. Poghosyan¹, Yevgeni S. Mamasakhlisov^{2,3}, Marine A. Parsadanyan⁴✉, Mariam A. Shahinyan⁴, Zvart H. Movsisyan⁴ & Poghos O. Vardevanyan⁴

The interaction between dopamine and RNA structures holds significant potential for understanding neurotransmitter-driven RNA modulation and biosensor design. Here, we employ all-atom molecular dynamics (MD) simulations to investigate the concentration-dependent binding of dopamine to poly(rA)/poly(rU) complex. We reveal that the dopamine molecules are preferentially trapped by poly(A)/poly(U) complex where the dopamine catechol rings became oriented parallel towards to RNA amine rings, although with the increase of dopamine concentration we track a multi-mode binding of dopamine molecules, i.e., different configurations can be found. The increasing of dopamine concentration leads to the dense packing of poly(A)/poly(U) complex, where more than half of dopamine molecules are strongly bound. We argue that the dopamine shows mainly intercalation mechanism of stabilization of poly(A)–poly(U) complexes governed by the hydrogen bonds network formation. These findings offer new insights relevant to RNA-based biosensors and the interplay between neurotransmitters and nucleic acids.

Keywords Molecular dynamics study, RNA, Poly(rA), Poly(rU), Dopamine, Neurotransmitter binding, Biosensors

Dopamine cognitive role is proven by its value not only in mental disorders, such as attention deficit hyperactivity disorder (ADHD) and Parkinson's disease, but also in healthy states of stress and fatigue that are resulted from cognitive control deficit¹. Even small fluctuations of dopamine concentration lead to huge and irreversible consequences in the brain, such as Parkinson's disease and schizophrenia^{2–9}. Proceeding from its irreplaceable importance and enormous damages for human mental and physical health, caused even at small concentration variations, it is actual to monitor its amount in the blood plasma and fix even very small alterations. However, today the techniques for dopamine concentration determination are intensively being searched^{10–21}. One of the approaches to achieve this goal is to create biosensors that will detect dopamine concentration. On the other hand, it is very important to determine which biological material will be chosen as an underlayer for such biosensors^{10,20,21}. In this study poly(rA)/poly(rU) complex was chosen as the possible underlayer for dopamine-sensor.

Dopamine in different forms (neutral, protonated and deprotonated) was intensively investigated using various type of experiments^{22,23}, as well as computational methods^{22,24–26}. It is known that at physiological pH, the dopamine exists mainly in its cationic form, assuming that this is the active form for transport^{27,28}. On the other hand, the theoretical calculations (ab initio molecular orbital study) also indicate that the dopamine is stable cationic molecule.

Different RNA/ligand complexes have been intensively studied^{2–29} to understand the binding properties and identify specific links between compounds. In this aspect, the ability of RNA to specifically recognize and tightly bind the dopamine molecules^{30,31} is important to figure out the high affinity of dopamine toward RNA. It is experimentally evidenced that RNA and DNA can detect dopamine²⁴; however, the conformation and orientation issues are important to understand.

In this regards, molecular dynamics (MD) simulation method is proven to be the unique tool to study the structural, orientation and dynamic features of complex structures. We employ a series of long scale MD runs to examine RNA/dopamine complexes at wide concentration ranges aimed at revealing the binding affinity

¹Laboratory of Bioinformatics, Institute of Informatics and Automaton Problems of NAS RA, P. Sevak 1, 0014 Yerevan, Armenia. ²Institute of Applied Problem of Physics, H. Nersisyan 25, 0014 Yerevan, Armenia. ³Research Institute of Physics, Yerevan State University, A. Manoogian 1, 0025 Yerevan, Armenia. ⁴Laboratory of Biophysics of Sub-Cellular Structures, Research Institute of Biology, Yerevan State University, A. Manoogian 1, 0025, Yerevan, Armenia. ✉email: marine.parsadanyan@ysu.am

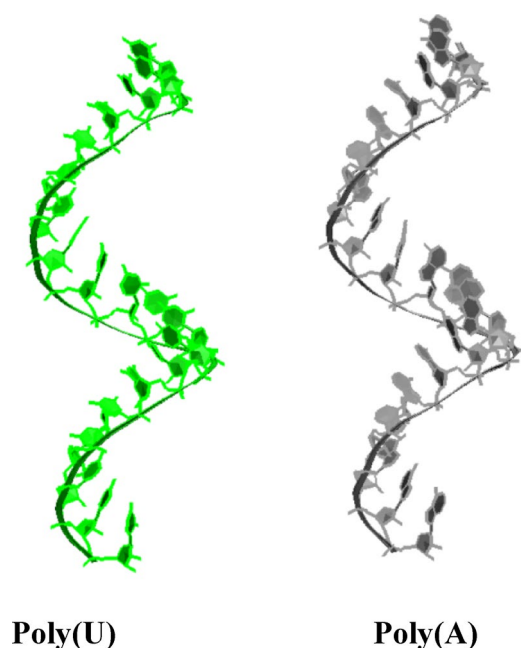


Fig. 1. All-atom presentation of poly(A) (grey) and poly(U) (green) molecules. The molecules were rendered as *Ribbons* using VMD package.

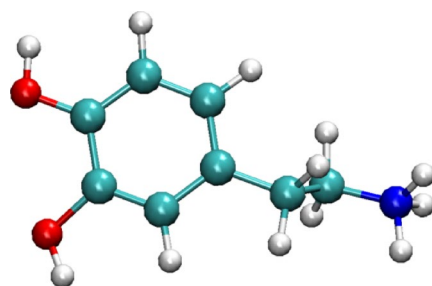


Fig. 2. The schematic presentation of cationated dopamine molecule. The molecule was rendered as CPK using VMD package. Colors are: nitrogen-blue, carbon-cyan, hydrogen-white and oxygen in red.

and orientation properties of dopamine, as well as at predicting the modes of binding of dopamine inside of poly(rA)/poly(rU) couple.

Methods: construction and simulation details

20-meric poly(A) and 20-meric poly(U) molecules were constructed using Avogadro equation³². The starting configuration is shown in Fig. 1.

The dopamine molecule was created, using *Ligand Reader and Modeler* tools available at CHARMM-GUI server³³. As an output, GROMACS compatible dopamine CHARMM36m force field was extracted from the same server³⁴. The schematic presentation of dopamine molecule was shown in Fig. 2. All MD runs were carried out, using the latest version of GROMACS software package³⁵ with CHARMM36m force field set³³. The water molecules were represented as TIP3P³⁶. In overall, five independent long-scale MD runs were performed at different dopamine concentrations and without dopamine (Control simulation/run), i.e. (i) control simulation—poly(A) and poly(U), (ii) 10 dopamine (0.016 M) molecules/poly(A)/poly(U) complex, (iii) 20 dopamine (0.033 M) molecules/poly(A)/poly(U) complex, (iv) 30 dopamine (0.049 M) molecules/poly(A)/poly(U) complex and (v) 50 dopamine (0.083 M) molecules/poly(A)/poly(U) complex. Note, that all simulations were done in the presence of 150 mM NaCl concentrations and in water bulk with a volume of $10 \times 10 \times 10 \text{ nm}^3$.

To equilibrate the system thermally, for each case, short simulations in NVT ensemble (6 steps by protocol) were carried out, according to the standard protocols, described in CHARMM-GUI server³³. Furthermore, each of 1000 ns production run at NPT ensemble was performed.

The MD protocols for all runs are: the room temperature and normal pressure was maintained, using Nose-Hoover³⁷ and Parrinello-Rahman³⁸ algorithms, respectively. The LINCS algorithm³⁹ was applied to maintain all bonds to their equilibration values. Particle Mesh Ewald (PME)⁴⁰ approach was applied to implement

electrostatic part with a cut-off of 1.2 nm and for the same cut-off it was also applied to calculate van der Waals interactions. The coordinates and velocities were saved every 0.2 ns and the time-step of production run was 2fs. For data analysis, GROMACS standard tools were used. The production runs for all cases were long enough and therefore, the replica runs to improve the statistics are not performed. The visualization and snapshots were done via VMD software package⁴¹.

All runs were performed on Armenian HPC infrastructure machine (“Aznavour” supermachine)⁴².

Results

First, we have checked the stability of the poly(A)/poly(U) complex, we calculated the root-mean-square deviation (RMSD), which is a quantitative measure aimed to assessing the accuracy of the simulation and the stability of the system. The RMSD curves are shown in Fig. 3. As one can see from RMSD curves, in the case of control simulation (without dopamine), we see the fluctuations till poly(A) and poly(U) come close to each other (~500 ns time-point) and form a complex. Poly(A)/poly(U) complex stays stable till ~800 ns time point and further, we see large fluctuations. Control simulation shows a maximum deviation of 3.5 nm, which is much higher compared to all structures with dopamine molecules. If we compare the structures with dopamine molecules, we see that the system with 20 dopamine molecules is the most stable, although one can mention that the system with 50 dopamine molecules exhibits a stability with a value of RMSD of ~2 nm.

Next, we evaluate the dimension and compactness of complex via calculation of radius of gyration of poly(A)/poly(U) system. For all runs, the radius of gyration curves was monitored in Fig. 4. Note, that the mentioned parameter was determined via GROMACS *gyrate* code. For control simulation, we see the same tendency as in the case of RMSD, i.e. the large fluctuations till 500 ns time-point and the stabilization until ~800 ns time-point. The R_g profiles in the case of dopamine molecules show that starting at ~100 ns time-points, the R_g is stable and the corresponding averaged values in the presence of 10, 20, 30 and 50 dopamine molecules are ~1.54 nm, 1.75 nm, 1.5 nm, and 1.72 nm. In the case of 30 dopamine molecules, the system is more compact with low R_g value, i.e. we track a dense packing of poly(A)/poly(U) complex.

Simultaneously, we have checked the distance between center of mass (C.O.M.) of poly(A) and poly(U). The corresponding profiles were monitored in Fig. 5. As one can see from profiles, the dense packing configurations mean small distances, which is obviously seen from the case of 30 dopamine molecules. In overall, the distances fluctuate from 1.5 to 2.5 nm in presence of dopamine molecules, while in control simulation, where there is no dopamine molecule, the distance between poly(A) and poly(U) is very large.

Thus, we argue that dopamine molecules lead to more compact packing of poly(A)/poly(U) complex.

To understand well the binding of dopamine molecules, we have calculated, so-called, the binding or “trapped” dopamine molecules. Note, that the parameter was calculated using in-house TCL script. The plots are shown in Fig. 6. At small concentration of dopamine molecules, we track that almost all molecules penetrated into RNA bulk, i.e. 10 and 20 dopamine molecules can incorporate into the complex, while the increase of dopamine to 30 and 50, only 60% of dopamine molecules are in the poly(A)/poly(U) complex.

To reveal the orientation features of dopamine molecules, we have carefully examined the trajectories of various runs. The snapshots extracted from different time-point of Control simulation are shown in Fig. 7. We see that the poly(A) and poly(U) dynamically come close to each other by forming a complex. The visual inspection of trajectories claims that the, so-called, stability time constant (or binding time constant) which is lifetime of forming/disorganization is roughly ~200–300 ns.

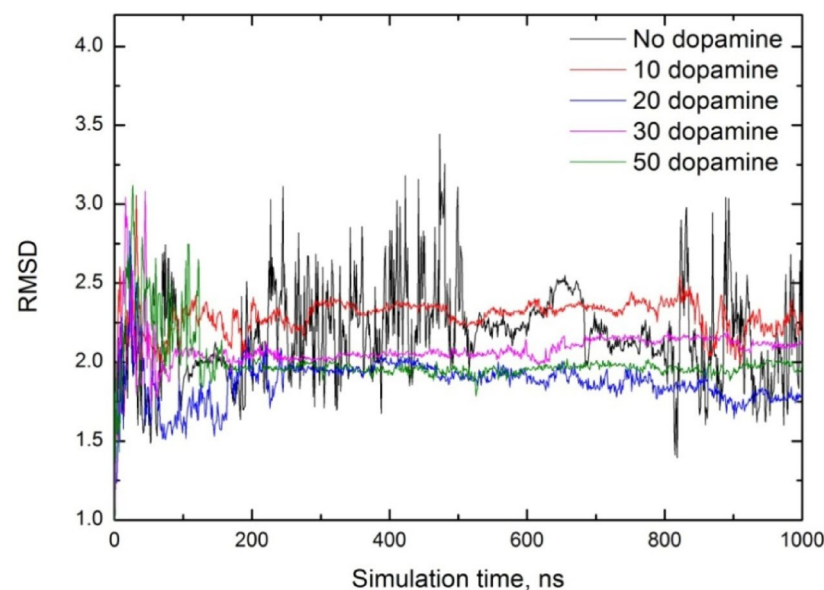


Fig. 3. The RMSD curve depending on simulation time for all cases of simulations.

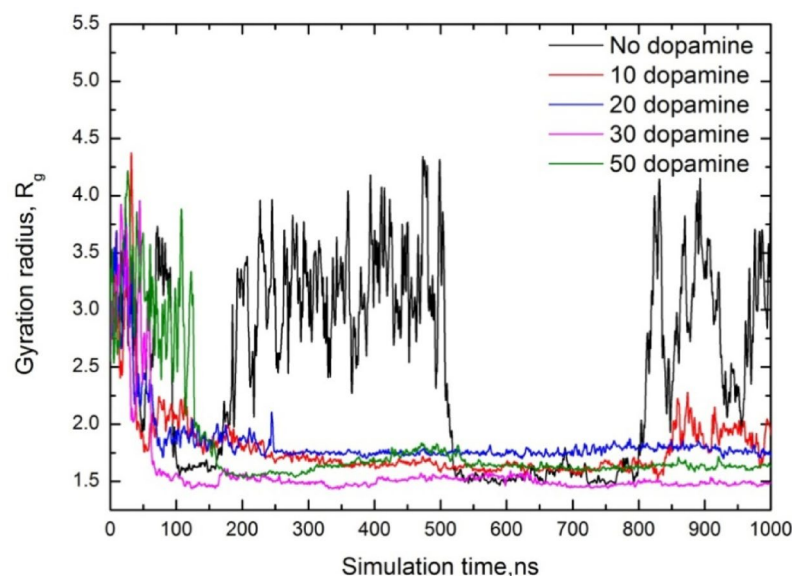


Fig. 4. The radius of gyration depending on simulation time for all series of runs.

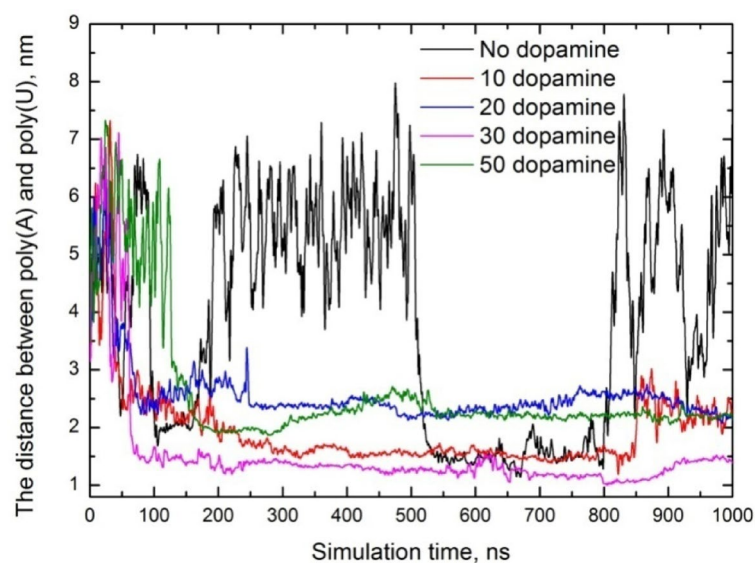


Fig. 5. The distance between C.O.M. of poly(A) and poly(U) depending on simulation time for all series of runs.

As you can see from the snapshots, at the end of simulation run, nine of ten dopamine molecules are trapped by poly(A)/poly(U) complex (see Fig. 8). Moreover, we track that four dopamine molecules bind to poly(U), while five molecules are capped by poly(A). Concerning the orientation of dopamine molecule, we see that the rings of dopamine are oriented parallel to poly(A) amine rings. DFT calculations⁴³ with the B97D/6-31 + G* basis set claim that between dopamine and RNA/DNA the interacting complexes are formed, where the interplanar angle between the plane of dopamine's aromatic ring and the plane of purine or pyrimidine is ranged from 6° to 47°⁴³. For clarity, the close view picture is shown in Fig. 9, extracted from the same last point of simulation. From the typical structure of the dopamine-poly(A) at the last time-point snapshot (see Fig. 10), we see that the mean distance between two rings is roughly 4 Å. In contrary to poly(A), the orientation of trapped dopamine molecules in poly(U) is not straightforward and we track different positions and no peculiarities in orientation point of view.

Analyzing the next run (20 dopamine molecules/poly(A)/poly(U)), we found the same orientation tendency, i.e. some dopamine molecules are oriented in a such way, where the dopamine rings are parallel to the poly(A) amine rings. The snapshot from the last point of simulation was shown in Fig. 11.

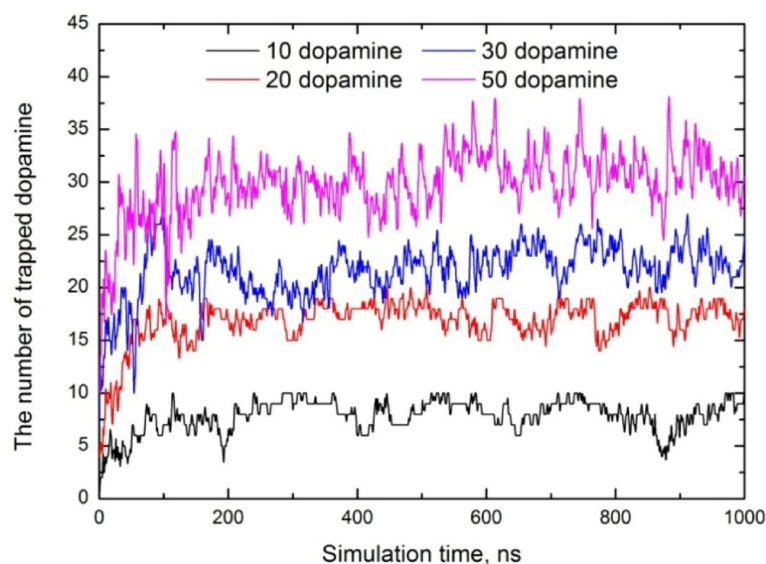


Fig. 6. The number of trapped dopamine molecules depending on simulation time for all series of runs.

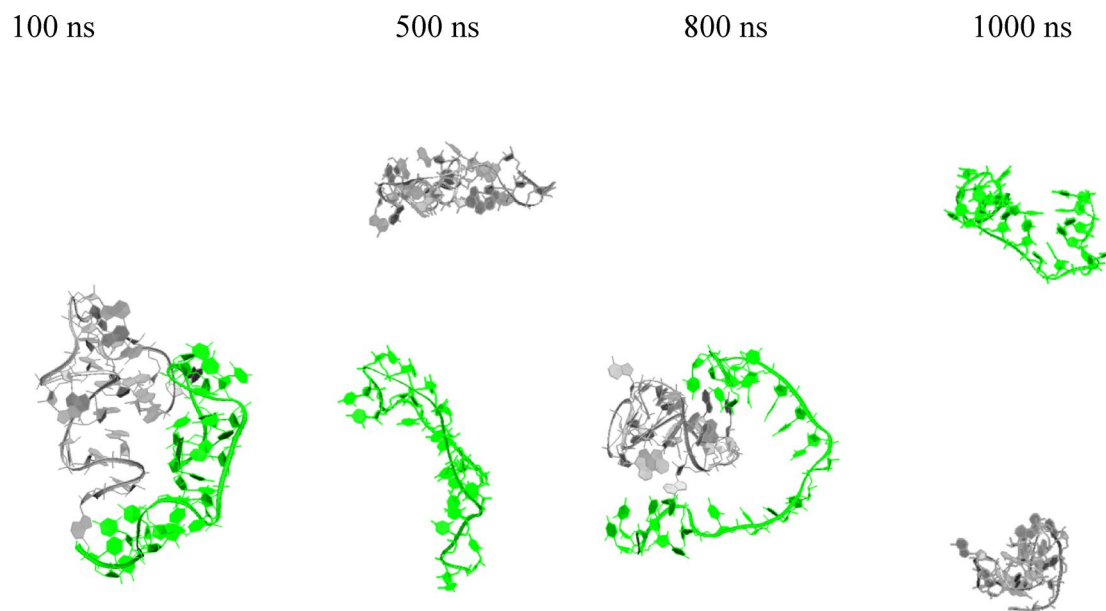


Fig. 7. The snapshots extracted from Control run (without dopamine) at different time-points. The next snapshot extracted from last time-point of 10 dopamine/poly(A)/poly(U) system is shown in Fig. 8. The snapshots were captured via VMD package. Colors are: poly(A)—grey, poly(U) — green.

Note, that parallel stacking is observed also in the case of poly(U), i.e. we see that some trapped dopamine molecules are oriented in such way as in the case of poly (A).

Increasing the dopamine concentration to 0.049 M (30 dopamine/poly(A)/poly(U) complex), we see more trapped dopamine molecules and the same orientation. The last point snapshot was shown in Fig. 12. Note, that in contrary to other concentrations, here, we have denser packing with lower R_g value (see also Fig. 4).

The increasing concentration of dopamine up to 0.083 M, we have the following picture (see Fig. 13), where the parallel stacking modes are also available.

Thus, we imply that the dopamine molecules are mostly oriented parallel to RNA amine rings and increasing the concentration of dopamine lead to the growth of parallel orientation modes. Note, that with the increase of the dopamine concentrations, some dopamine molecules were intercalated into a core of poly(A)/poly(U) complex.

To estimate the hydrogen bond effect we figure out the different cases, including the hydrogen bond network between dopamine and water— $\text{HB}^{\text{DOP-WAT}}$, dopamine and RNA— $\text{HB}^{\text{DOP-RNA}}$, poly(A) and poly(U)—

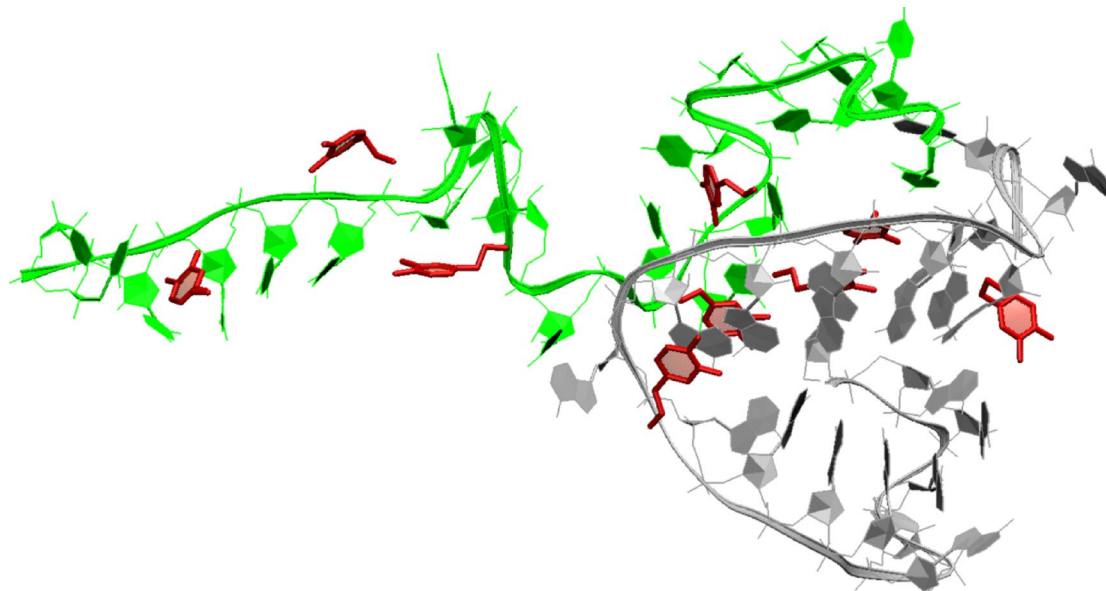


Fig. 8. The snapshot extracted from the last point of 10 dopamine/poly(A)/poly(U) system (1000 ns). Colors are: poly(A)—grey, poly(U)—green, the dopamine molecules are in red. The visualization was done by VMD package.

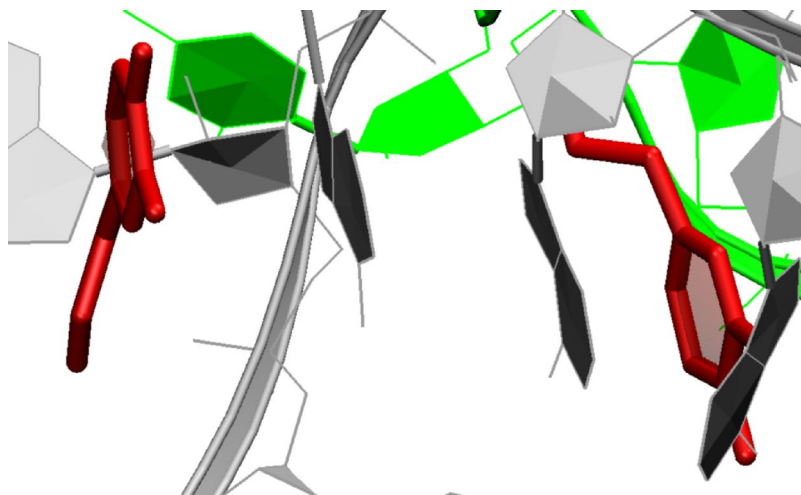


Fig. 9. Zoom on binding sites. The part of snapshot extracted from the last point of 10 dopamine/poly(A)/poly(U) system (1000 ns). Colors are: poly(A)—grey, poly(U)—green, dopamine molecules—red.

$\text{HB}^{\text{Poly(A)-Poly(U)}}$ and RNA and water— $\text{HB}^{\text{DOP-WAT}}$. Hydrogen bonding plays a key role in stabilizing dopamine-receptor complexes. The hydrogen atoms from catechol hydroxyl groups and the protonated amine (NH_3^+) group in dopamine are capable of forming hydrogen bonds when acting as donors^{44,45}. Note, that the hydrogen network formed by amine hydrogens is much stronger than those formed by catechol phenolic hydroxyls⁴⁴. On the other hand, the oxygen atoms of dopamine also can be employed to form a hydrogen bonds, i.e. dopamine is considered as an acceptor^{25,44}.

In Fig. 14, all possible cases to estimate the hydrogen bond network, were monitored. Note, that all plots were calculated via GROMACS *hbond* module.

As expected with the increase of dopamine concentration, we track the increase of hydrogen bonds between dopamine molecules and water. The data indicate the hydrogen bond network between NH_3^+ group and water, as well as between dopamine's OH and water. The number of water molecules around the dopamine's NH_3^+ and OH groups is estimated to be $\sim 2-3$, which is in good agreement with similar results⁴⁶. In the case of $\text{HB}^{\text{DOP-WAT}}$, the results show that the increase of dopamine concentration leads to reducing the number of bonds formed between RNA and water molecules. Discussing the poly(A)–poly(U) contacts, we see that in the case of control simulation (without any dopamine molecules), the hydrogen bonds appear, when poly(A)/poly(U) complex is formed and disappear, when two species are far from each other, when the lifetime of hydrogen bonding is

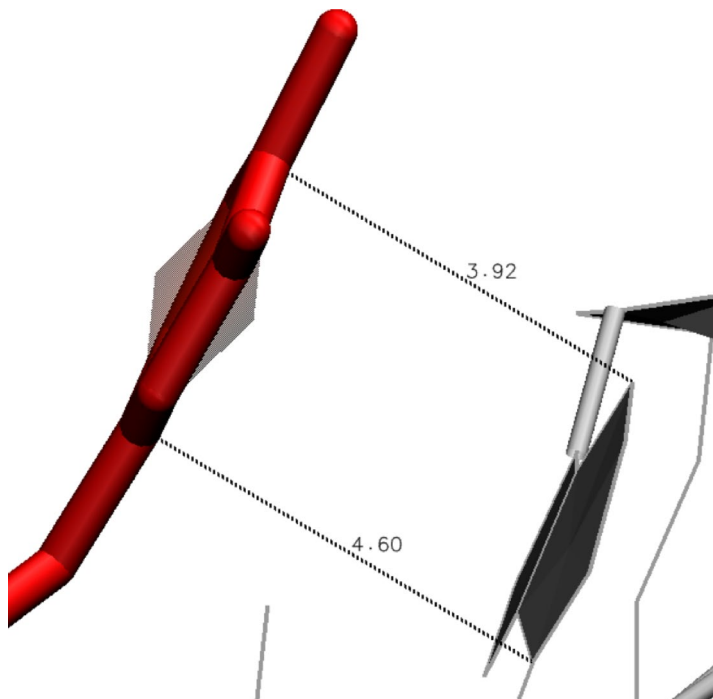


Fig. 10. Representative structure of dopamine/poly(A) pair captured at 1000 ns snapshot of 10 dopamine/poly(A)/poly(U) system. The distances are in Angstroms. Colors are: poly(A)—grey, dopamine molecules—red.

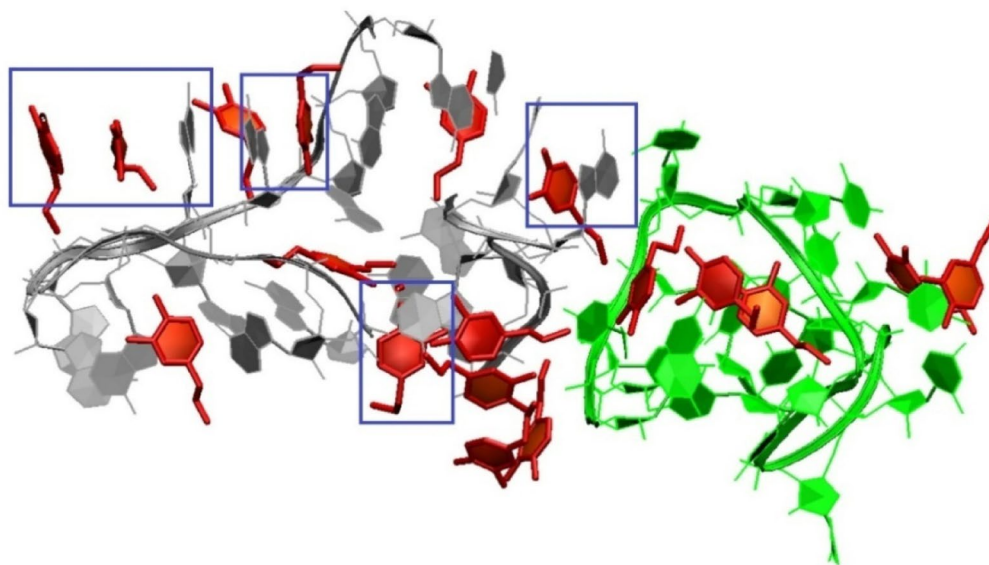


Fig. 11. The snapshot extracted from the last point of 20 dopamine/poly(A)/poly(U) system (1000 ns). Colors are: poly(A)—grey, poly(U)—green, the dopamine molecules are in red. The parallel stackings are labelled as blue rectangles. The visualization was done by VMD package.

estimated to be ~200–300 ns as clearly seen from the previous data (see snapshots in Fig. 7). Note, that there is no peculiarity, when the dopamine concentration increases, however, one can see that in the case of 20 and 50 dopamine molecules, the number of H-contacts between poly(A) and poly(U) is reduced. Considering the dopamine-RNA case, one can argue that with the increase of dopamine concentration, the H-contacts with RNA increases, moreover, we argue that both catechol phenolic hydroxyls and hydrogens at NH_3^+ groups are involved in H-network. For clarity, we show the fragmental snapshot, extracted from the last point of 10 dopamine/poly(A)/poly(U) system, where two H-bonds cases are shown (Fig. 15).

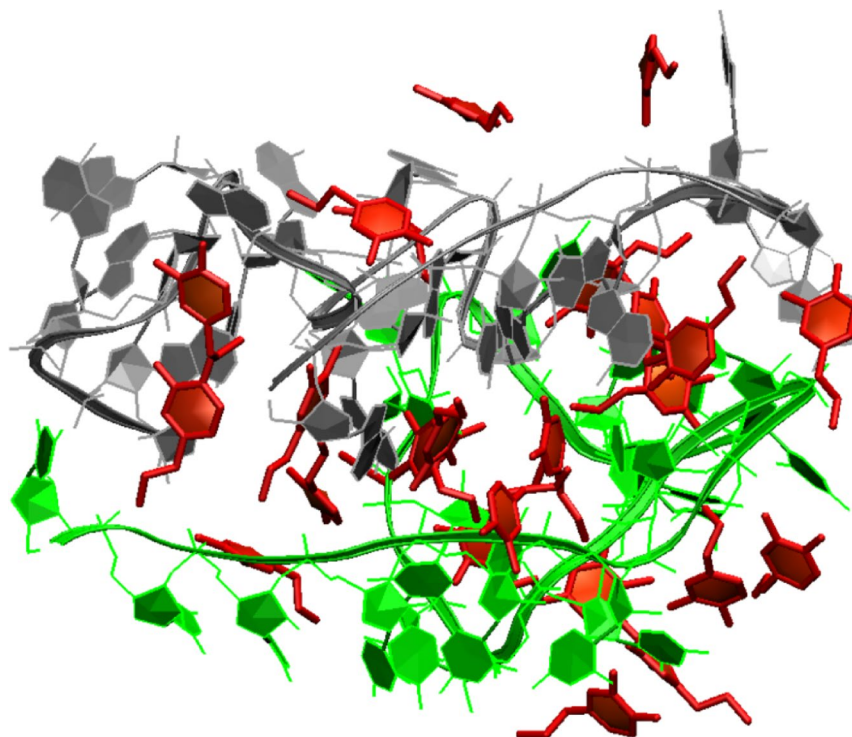


Fig. 12. The snapshot extracted from the last point of 30 dopamine/poly(A)/poly(U) system (1000 ns). Colors are: poly(A)—grey, poly(U)—green, the dopamine molecules are in red. The visualization was done by VMD package.

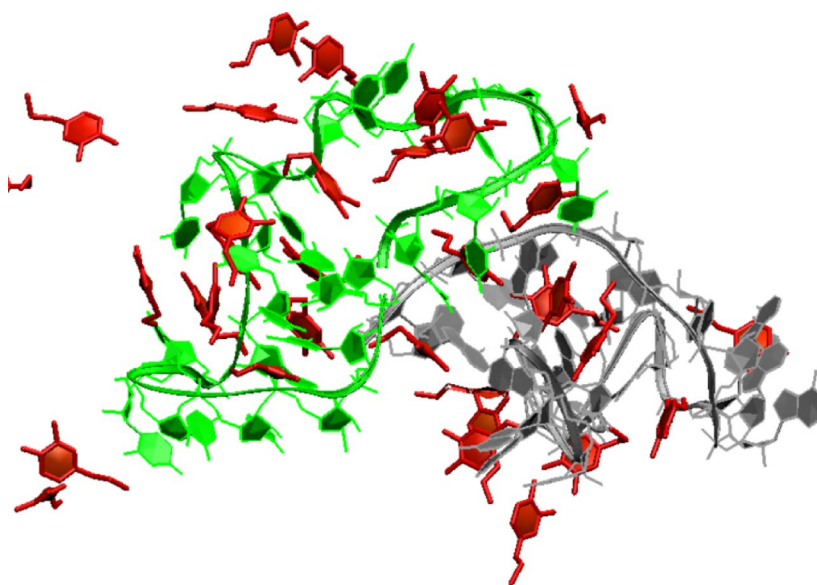


Fig. 13. The snapshot extracted from the last point of 50 dopamine/poly(A)/poly(U) system (1000 ns). Colors are: poly(A)—grey, poly(U)—green, the dopamine molecules are in red. The visualization was done by VMD package.

Conclusion

We have performed MD simulation of poly(A)/poly(U) complexes in the presence of cationated dopamine at physiological conditions. A series of long-scale runs were carried out on dopamine/poly(A)/poly(U) complexes, where the wide concentration range of dopamine is considered. We see, when the dopamine molecules are added to the poly(A)/poly(U) system, the latter becomes more compact, i.e. the increasing of the dopamine concentration leads to more dense packing of poly(A)/poly(U) complex. In control run, the poly(A) and poly(U)

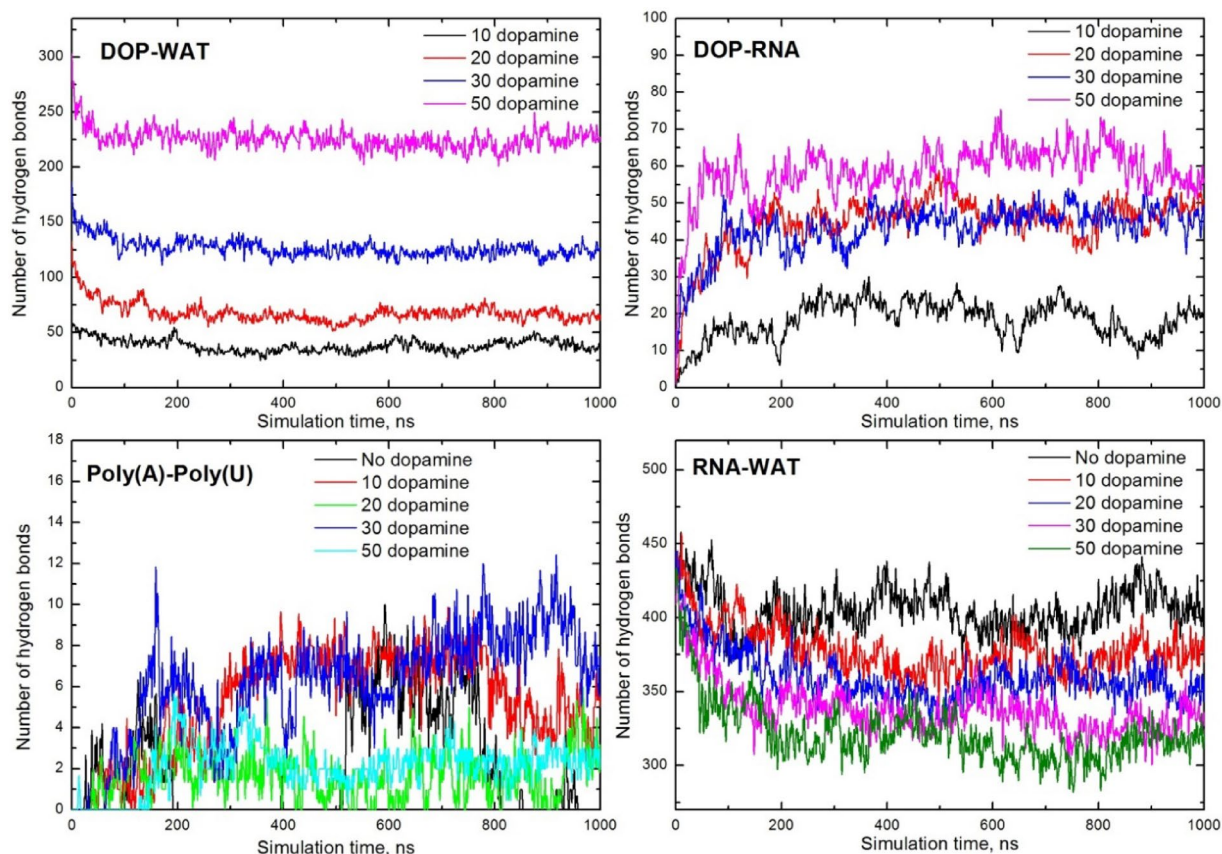


Fig. 14. The number of hydrogen bonds depending on production runs for different cases.

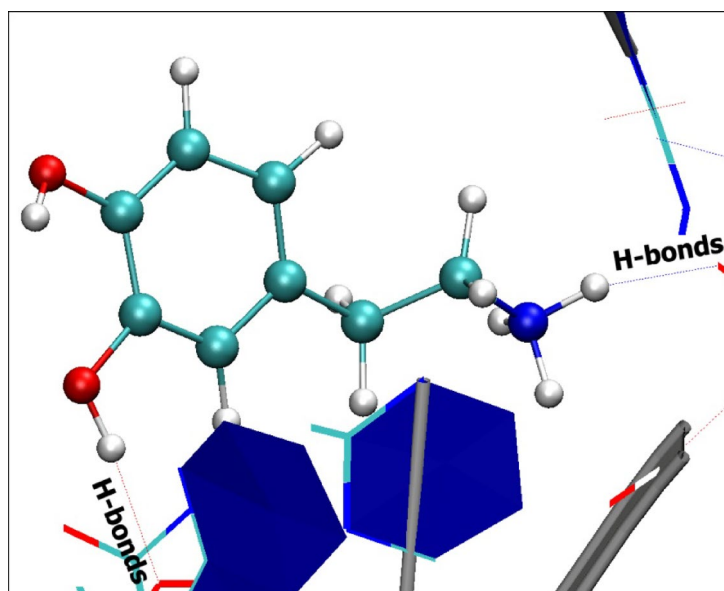


Fig. 15. Zoom on one of dopamine molecule in the part of snapshot, extracted from the last point of 10 dopamine/ poly(A)/poly(U) system (1000 ns).

molecules are periodically organized and disorganized in the complex, and the stability time constant (or binding time constant), which measures the time, when two compounds come together to form the complex, is roughly ~ 200 – 300 ns. Adding the dopamine to the system leads to the stabilization of the complex and when at the beginning of run the poly(A) and poly(U) form a complex, they remain stable over all course of production

run. Thus, we argue that the compact structure of the poly(A)/poly(U) complex is stabilized by the binding of dopamine molecules, i.e. the dopamine molecules serve as a linkage between two RNA molecules. In fact, RNA-dopamine hydrogen bonds are partially displaced by the RNA-RNA hydrogen bonds.

When concentration of dopamine increases, the number of trapped molecules increases and at some point, the saturation occurs, when about half of dopamine (0.083 M) molecules bind to the poly(A)/poly(U) complex.

Discussing the orientation of dopamine molecules, we argue that most of them are oriented in parallel, i.e. the dopamine ring is parallel to RNA amine group, where the average distance between rings is roughly 4 Å.

The poly(A)/poly(U) complex is stabilized by hydrogen bonds, formed between RNA and dopamine molecules, where both hydroxyls of the catechol moiety and hydrogens at NH_3^+ groups are involved in hydrogen network. According to the hydrogen bond results, we see that the dopamine exhibits mainly intercalation mechanism of stabilization of poly(A)–poly(U) complexes, accompanied by the hydrogen bonds formation between RNA and dopamine molecules, suppressing formation of hydrogen bonds between RNA–water.

Data availability

All data generated or analysed during this study are included in this published article. Besides, some supporting materials (coordinate files) from this study are available at www.bioinformatics.am for validation and further use.

Received: 11 February 2025; Accepted: 10 June 2025

Published online: 01 July 2025

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Acknowledgements

We thank for the computational resources (“Aznavour” HPC) provided at the Institute of Informatics and Automation Problems of NASRA.

Author contributions

All authors contributed to the study. Armen Poghosyan and Yevgeni Mamasakhlisov designed and performed the experiments. Armen Poghosyan wrote the first draft of the manuscript and all authors commented on the previous version of the manuscript. Mariam Shahinyan wrote the introduction part and designed the manuscript. Armen Poghosyan, Yevgeni Mamasakhlisov, Zvart Movsisyan and Marine Parsadanyan conceptualized, read, edited and designed the final manuscript. Poghos Vardevanyan supervised the manuscript. All authors approved the final version of the manuscript.

Funding

This research was supported by the Higher Education and Science Committee of MESCS RA (Research project № 24WS-1F011).

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to M.A.P.

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