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A Putative Quantum Transition in Zinc Atoms of Flavivirus Polymerase

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ABSTRACT

Metal ions are coordinated in many proteins, and zinc ions are an obligatory attribute of several important protein families. Rna-dependent RNA polymerase (RdRp) in viruses of flavivirus genus contains two zinc atoms located in the two specific zinc binding sites. A reason which can explain a presence of zinc ions in the proteins is not as clear as for ions of another metals. A quantum transition in zinc ions is allowed and by a proposed suggestion it is utilized to arrange synchronous transformations of the coordinating proteins via a quantum entanglement. Molecular dynamics experiments which were conducted for flavivirus NS5 protein suggest that the conformation of the RdRp domain in NS5 is highly sensitive to the bond lengths between the zinc atoms and their four coordinating atoms. We hypothesize that a change of conformation is required for the functioning of the viral replicative complex and that it is the quantum transition in the zinc atoms which slightly changes the bond lengths; thus assisting the switch between the conformations. The deterministic induction of the transition in a virus replication can be explained by a quantum entanglement of the zinc atoms with some another quantum system.

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Introduction

Metal ions are bound to many proteins in living cells. Iron ions are coordinated in hemoglobin, the protein which is able to keep oxygen and transfer it across a body. Magnesium or manganese ions are coordinated in a reaction center of chlorophyll. A narrow energy gap between quantum states of these ions is utilized in a cell in a variety of catalytic processes.

A role of quantum effects in living systems is seen closer if functions of metal ions in pro-teins are considered. Quantum transitions in these systems which are of crucial importance to a function of a cell can be assumed only at a qualitative level and are beyond a precision of numerical calculations.

A role of electron transfer in a catalysis is easily interpreted at a qualitative level for ions of iron or magnesium. These ions meet often in proteins; iron is always bounded to proteins of cytochrome family, magnesium atom is often utilized to arrange oxidation of nucleotides in a catalytic center of polymerases.

Zinc ions are also bound to some proteins as an essential component. A so-called "zinc-finger" family of transcription factors which is widely represented in human genome always include a site of a zinc-binding pocket. And a pair of zinc atoms is always bound in an eplicative complex of viruses from *flaviviridae* family.

Flaviviridae is a family of RNA viruses, it includes virus of hepatitis C (HCV) and a number of species from *Flavivirus* genus. Tick-borne encephalitis virus (TBEV), Japanese encephalitis virus (JEV), Dengue virus are among these viruses. Almost all species of RNA viruses and phages include a gene of RNA-dependent RNA polymerase (RdRp). RdRp protein has a highly conservative structure across all of these species. The direct function of this protein is to catalyze the replication of viral RNA.

Several sequence motifs in RdRp which are essential for a polymerase function have the same structure across many species. Moreover, all viruses have a catalytic mechanism for nucleotide insertion which requires two metal ions coordinated to two side chains of aspartic acid.

While the catalysis itself is assisted by the specific ions and residues in the active center of the polymerase, the whole replicative complex of flaviviridae family is always combined from the polymerase and several auxiliary proteins. In flavivirus genus the RdRp is one of the domains of a protein encoded by the NS5 gene. Another domain of this protein has a methyltranferase activity, which is required for capping of RNA in an initial phase of a replication.

Several structures have been determined for flavivirus RdRp and for a whole NS5 protein [1–5]. A mutual orientation of the two domains in a full-length NS5 protein is unstable, and two phases of orientation have been obtained in crystallographic experiments. One phase is represented in structure 4v0r [3], for the Japanese encephalitis virus protein. This phase corresponds to a state of the

polymerase activity, and the another phase which is represented in a number of structures corresponds to methyltransferase activity, as it was suggested in [7].

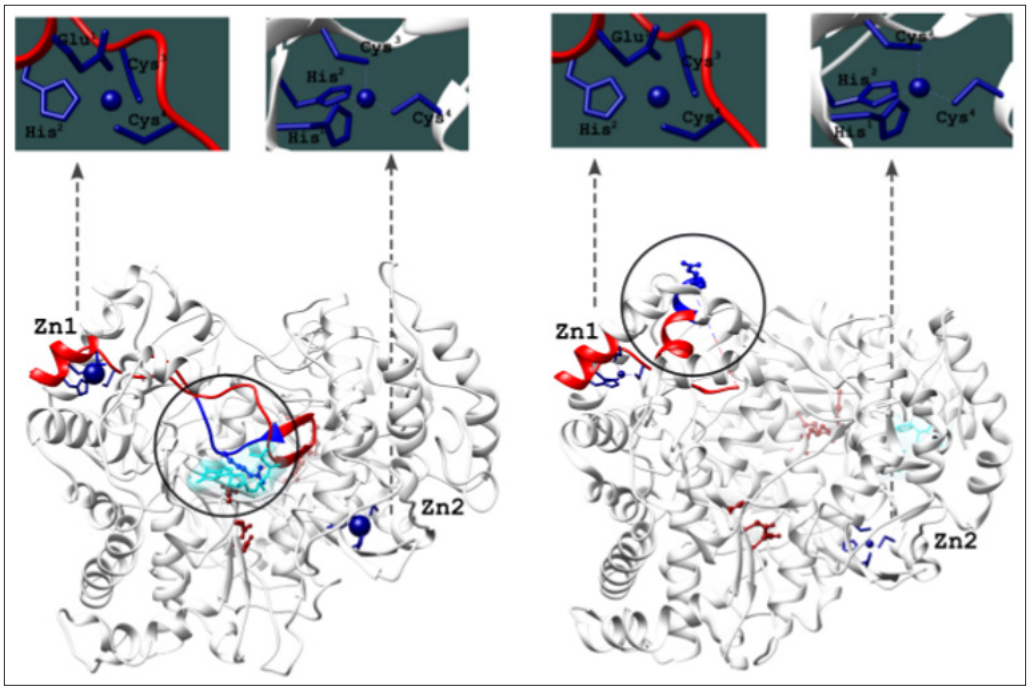

Figure 1: Zinc-binding pockets in polymerase domain of flavivirus NS5 protein. Left: active phase of polymerase. Right: inactive phase of polymerase. Segment of chain shown in blue and red corresponds to conservative motif F [6,7]. GTP molecule in the active center of the polymerase is shown in cyan.

The presence of zinc ions in the polymerase domain is detected in crystallographic studies, two zinc ions are bound in the so-called "binding pockets" (fig. 1). The regions which correspond to the zinc binding pockets are highly conservative in species of flavivirus genus as well as another structural motifs of NS5 protein. Each of the two zinc ions is coordinated by side chains of four amino acid residues, usually two cysteines and two histidines or one histidine and one aspartic acid. The electron configuration of each of the zinc atoms corresponds to sp3 hybridization, so that the protein atoms which coordinate the zinc ions are located it the vertex corners of a tetrahedron.

Results and Discussion

The electron configuration of a zinc ion in a protein allow quantum transitions between levels of d-orbital (fig.2). The energies of these transitions are expected to be comparable with energies of stochastic movements in a system.

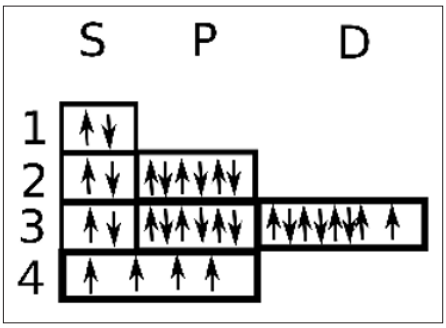

Figure 2: Electron configuration of a zinc ion when it is coordinated in a protein

The lengths of coordinating bonds of zinc ions are within an interval of 2.2 ± 0.2 angstroms in the available X-ray structures. The assumed quantum transitions can lead to some changes of the bond lengths within this level of precision.

A series of molecular dynamics simulations was carried on for NS5 protein of Japanese encephalitis virus in a phase of polymerase catalytic activity. Bond lengths for zinc ions were varied from 1.45 to 2.2 angstroms. It was observed for marginal values of bond lengths that the overall structure of the RdRp domain is sensitive to small perturbations in the zinc-binding pockets.

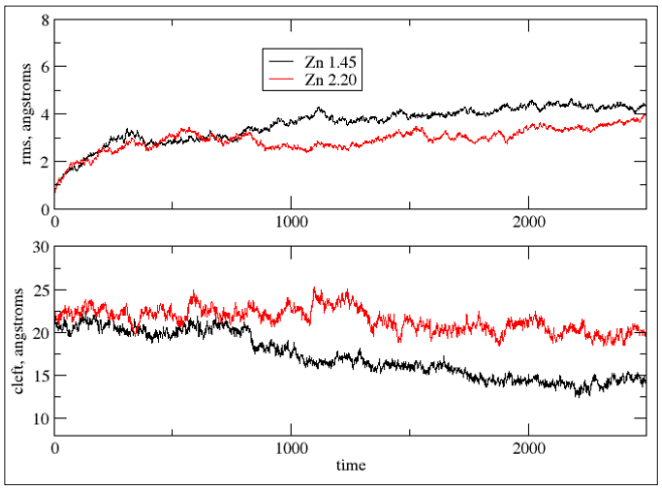

Figure 3: Trajectories of dynamics in marginal values of coordinating lengths

The structure of polymerase is by a convention compared with right hand [9]. The observed changes in an orientation of subdomains in polymerase are similar to opening and closing of the hand (fig. 3). So, the hypothesis is suggested that a quantum transition in zinc ions is an obligatory part of a role which these ions play in a functioning of polymerase. This transition is deterministically induced in each round of polymerization, and is probably mediated

by quantum entanglement with some other quantum system.

The bottom margin of the bond lengths in the simulations was far below the acceptable interval. From another side, the changes of structure for such a small bond lengths were observed in less than 20 ns. This time interval is within a limit in which runs of molecular dynamics remain close to reality, and the movements in simulations occur much faster than the it can be expected to happen in a real protein. A changes of bond lengths within 0.2 angstroms due to a quantum transition can easily be assumed. The sensitivity of a polymerase structure to perturbations in zinc binding pockets is anyway observed in the simulations.

The template of RNA is kept in the "hand" of polymerase in a phase when it is in an active state. An ability to open and close the hand should be therefore an allowed direction of RdRp flexibility. The need for these movements to be deterministically induced is implied in the role which the polymerase do play in a virus replication.

An energy of the expected transition is not too large and the transition can occur by chance. Another opportunity which can explain an induction of the transition is a quantum entanglement of zinc atoms with some another subsystem.

A stochastic quantum transition in a zinc ion is not expected to contribute too much in ordinary stochastic movements of atoms in the protein. A role of zinc ions in the protein is in this case in some stabilization of a structure, as it is assumed in a conventional viewpoint.

A suggested quantum entanglement of zinc ions does not allow to guess an another subsystem which is bound to the transitions in these ions. An advantage of this hypothesis is that the assumed transitions occur due to more deterministic reasons and a role of zinc ions becomes therefore more specific than in a conventional interpretation.

Genes which are responsible for a replication in hepatitis C virus differ the homologous genes in flaviviruses. There, the two zinc ions are coordinated in the two subunits of NS5B protein. These subunits are bound in a replicative complex with NS5A polymerase in which zinc-binding sites are missed. A possibility of quantum transitions caused by a similar entanglement is anyway conserved in HCV replication.

An obligatory presence of a zinc ion in "zinc-finger" transcription factors can also be interpreted in a similar way. A role of any transcription factor is to bind to a suitable site in DNA chain. A need to switch a conformation between mode of search and mode of recognition was assumed for transcription factors in order to explain a relatively short time in which they find a proper location in DNA [8]. And a quantum transition in a zinc atom of "zinc-finger" domain do possibly induce this switch between conformations, due to a similar quantum entanglement with some another subsystem.

The another quantum subsystem or a chain of subsystems which are coupled in the entanglement with zinc ions is unspecified in the proposed hypothesis. The extent in which the transformations which accomplish a replication of viral RNA are synchronized also remains unknown.

But all the suggested effects are anyway within the limits of rationality and are vital for a proper fu nctioning of a cell or a virus. An so, the presented viewpoint do stress a role which quantum entanglement can have in common and ordinary events in living systems.

Methods

Amber12 package was used for molecular dynamics simulations [10]. Four equalized bond lengths were set to the same value in force field parameters for zinc atoms. The value of the lengths was varied on different runs and all other parameters of the force field were kept the same. A series of simulations was conducted to approve the declared result.

A stabilization of the system was performed before a productive run in each simulation, following a conventional routine described in [11]. The relative movement of subdomains was stably observed in the trajectories. The size of "cleft" between "fingers" and "thumb" is shown in fig 3 as a qualitative representation of the observed movements. It was calculated as the distance between groups of atoms in these two subdomains.

An alignment of zinc-binding sites for several species from flavivirus genus in fig 4 and the lengths of coordinated bonds for zinc ions in table I are provided below for a reference.

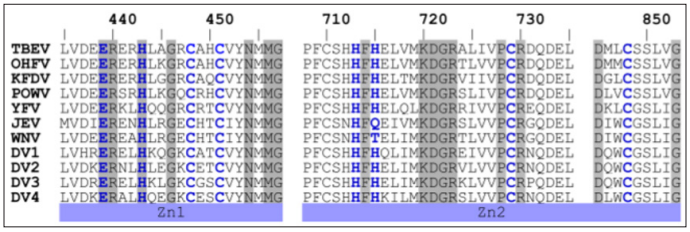

Figure 4: Alignment of two zinc-binding sites of consensus NS5 sequences of the flavivirus genus. Coordinating residues are marked with blue, highly conservative residues are marked with gray boxes. Numeration of the residues is that of the Tick-borne encephalitis virus (TBEV) NS5 protein

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