MAR05-2004-005022

Abstract for an Invited Paper
for the MAR05 Meeting of
the American Physical Society

A double-ratchet mechanism of transcription elongation and its control[1]

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Transcription, the process by which the genetic information encoded in DNA is transferred into RNA, is the first step in gene expression and it is the step at which most regulation occurs. A detailed understanding of the structural and mechanistic aspects of each step of transcription (initiation, elongation, termination and regulation) is one of the holy grails of biology. Here we characterize the motion of RNA polymerase (RNAP), the multi-subunit molecular motor that carries out the transcription process, during the elongation stage. We argue that during elongation RNAP moves by a complex Brownian ratchet mechanism in which the translocation along DNA and the binding of nucleotides into RNAP's catalytic center are coupled to a fluctuating internal degree of freedom associated with a protein sub-unit (the F-bridge) of RNAP. More precisely, the model is defined by a set of kinetic equationsdescribing the competition for the catalytic site between an incoming nucleotide, the 3'-end of RNA, and the F-bridge which in its bent conformation blocks the active center. An important aspect of the model is the incorporation of the three "active" processes describing (i) the ejection of bound nucleotides from the active center through steric clashes with either the F-bridge in its bent conformation or with the 3'-end of RNA; and (ii) the forward translocation induced by bending of the F-bridge pushing against the 3'-end of RNA. The "active" processes do not imply a "power stroke" mechanism since the energy driving them is purely thermal. Indeed the model displays a route by which the system uses thermal fluctuations to control the rate, processivity and fidelity of transcription already before the irreversible chemical incorporation step. Moreover, the model qualitatively explains many aspects of both bio-chemical[2] and kinetic[3] experiments on transcription elongation in *E-coli* and makes a number of falsifiable predictions.

[1]This work was done in collaboration with Daibhid O'Maoileidigh from the Department of Physics and the BioMaPS Institute at Rutgers and Evgeny Nudler's group from the Department of Biochemistry at the NYU Medical Center

[2]Bar-Nahum, G., Epshtein, V., Ruckenstein, A.E., Rafikov, R., Mustaev, A., and Nudler, E. A ratchet mechanism of transcription elongation and its control. To appear in Cell, 2005.

[3]Holmes, S.F., and Erie D.A. Downstream DNA sequence effects on transcription elongation. Allosteric binding of nucleoside triphosphates facilitates translocation via a ratchet motion. J Biol Chem. 278, 35597-35608.