INDRAPRASTHA INSTITUTE *of*
INFORMATION TECHNOLOGY **DELHI**

Invitation to M.Tech. Thesis Defense of Ghanendra Singh : August 20, 2021 (Friday): 16.00-17.00 IST

In Partial Fulfilment of the Requirements for the Degree of

M.Tech. CB

Ghanendra Singh (MT19213)

Will defend his thesis

Title: "**Modeling the dynamics of Telomere End Replication**"

IIIT-D Faculty and Students are invited

Date: August 20, 2021 (Friday)
Time: 16.00-17.00 IST
Online over Google meet (https://meet.google.com/wex-drcf-tor)

Examiner:	**Internal:**	**Ganesh Bagler**
	External/~~Internal~~:	**S. Ramachandran, IGIB**
	Advisor:	**K. Sriram**

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Abstract

Telomeres are the repetitive non-coding nucleotide sequence with specialized proteins at the end of the chromosomes that protect them from fusion and damage. During the late S phase of DNA replication, telomeres are shortened due to the end replication problem and elongated by telomerase. Cells maintain homeostatic telomere length, and this homeostatic disruption leads to various types of diseases. Presently, it is not clear how telomeres achieve homeostasis. One of the prevailing hypotheses is a protein-counting model with an in-built sensor mechanism that counts proteins that directly regulates the telomeric length. However, the dominant protein counting model for regulating telomerase access to elongate the telomere proposed earlier does not explain the latest experimental findings and evidence of DNA replication in telomere length regulation. Recently, Carol Greider put forward another hypothesis pitching for the role of replication fork in maintaining telomere length homeostasis. This replication fork model explains the role of DNA replication and firing of replication origins in telomere length regulation. It also provides insight into the underlying mechanisms that regulate telomere length at the molecular level. Based on these hypotheses, in this thesis research work, we first present a mathematical model based on the underlying molecular mechanisms of length regulation needed to establish telomere length homeostasis with yeast as our model organism. We perform both deterministic and stochastic simulations to validate the models with the experimental data of Teixeira et al., and we also used rate-balance plot, and phase plane analysis of the model to understand the nature of dynamics. For global analysis, we constructed bifurcation diagrams. The model explains the role of negative and positive feedback loops and a delay between telomerase and telomere-bound proteins, leading to oscillations in telomere length. We map these in-silico results to Teixeira's proposition of telomeres making a transition between extendible and non-extendible states. Finally, an attempt has been made to model and explain the hypothesis proposed by Greider, the replication fork model. Through our preliminary modeling studies, we try to explain the importance of replication fork progression and its role in telomere length regulation.