ID de Contribution: **4** Type: **Non spécifié**

Numerical model of checkpoint dependent replication origin activation in the Xenopus in vitro system

The initiation of DNA replication in multicellular organisms begins at thousands of genomic positions known as replication origins, which are activated at different times during the S phase in a regulated manner. Furthermore, few origins are grouped into so-called replication clusters that fire more or less synchronously. Previous studies point out that in the *Xenopus in vitro* system the ATR-Chk1 dependent checkpoint pathway is necessary to globally inhibit origin activation in the presence and absence of exogenous replication stress. Using DNA combing we showed that checkpoint inhibition did not lead to the inhibition of origins in already activated replication clusters, close to stalled forks.

The stochastic nature of the initiation process together with limitations of the experimental techniques, require the use of numerical models to obtain more information about the spatial and temporal activation of replication origins.
To this purpose, I tested different models by comparing Monte Carlo simulations and data from DNA combing experiments in the presence and absence of Chk1 inhibition. I used a genetic algorithm which allows to optimize the fitting of the multitude of different replication parameters. The best accordance with experimental data was obtained with a model that combines three notions: 1) a random initiation by an increasing limiting factor, 2) a strong global inhibition of origins firing by Chk1 protein and 3) an enhanced initiation probability near active replication forks together with a local repression of the Chk1 action. The model is consistent with the fact that replication origins are grouped into different temporal clusters. Combining numerical simulations with new models and experimental data will allow us to develop a new global model of the replication program in eukaryotes.

Authors: CIARDO, Diletta; GOLDAR , Arach; MARHEINEKE, Kathrin

Orateur: CIARDO, Diletta