A model for cell division dynamics leading to senescence

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Telomeres, regions of highly repetitive –and therefore a priori non-coding– DNA sequences capping the end of eukaryote chromosomes, are essential in maintaining genomic integrity by protecting chromosome extremities. Unavoidable consequence of the end-replication problem, chromosomes indeed shorten with every round of replication which would result, in absence of non-coding telomeric sequences, in the loss of coding DNA sequences essential to cellular function.
A dedicated enzyme called *telomerase* is however able to counterbalance telomere systematic shortening by elongating them. When telomerase is not expressed though, as in human somatic cells or in experimentally mutated cells, telomeres shorten until reaching a minimum length (the Hayflick limit) recognized as DNA damage which triggers *replicative senescence* –a generally irreversible arrest in the cell-cycle– and eventually leads to death of the cell.
If replicative senescence protects organisms from unrestricted cell proliferation, it is characterized by a high level of heterogeneity –still not well-understood– which promotes genome instability and senescence escape. In particular, some cells manage to escape senescence or even maintain their telomeres in absence of telomerase –the ALT-mutants implicated in 10%–15% of cancers.

In this poster, we first present a model for cell dynamics in absence of telomerase and ALT-mutant, taking into account telomere shortening with a mechanistically-based description formulated in [1]. It also accounts for the experimentally observed variability in the senescence onset through a more phenomenological description based on [2]. The model is supported by experimental data as well as numerical simulations of both cell lineages (one daughter tracked at each cell division) and cell populations, all presented in a second part. Simulations also allow prediction on the evolution of non-experimentally accessible data. In a third part we discuss how to include ALT-mutants in the model.

[1] S. Eugène, T. Bourgeron, Z. Xu. *Effects of initial telomere length distribution on senescence onset and heterogeneity.* Journal of Theoretical Biology, **413**, 58–65, 2017. doi :10.1016/j.jtbi.2016.11.010.

[2] H. Martin. *Étude de données et analyse de modèles intégro-différentiels en biologie cellulaire.* Ph.D. thesis, 2019.

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