Probing the senescence-induced senescence hypothesis

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Contents

1 Introduction

Cellular senescence can be thought of as a form of cellular purgatory. Senescent cells can no longer divide but continue to limp along rather than apoptose. In young, healthy organisms, senescent cells can play a positive role in arresting tumor growth and healing wounds (Ricón 2020; He and Sharpless 2017; Krtolica et al. 2001). However, increasing evidence points to senescent cells contributing to the aging process via slowing stem cell growth and tissue regeneration and increasing inflammation in older organisms (Campisi and Di Fagagna 2007).

A characteristic pattern that accompanies this shift is an increase in relative abundance of and slowing down of turnover of senescent cells. Understanding and intervening on cellular senescence requires unraveling the puzzle behind why this occurs as organisms age. Evidence from Nelson et al. (2012) suggests that this process partly results from a "bystander effect" in which senescent cells induce nearby healthy cells into senescence (senescence-induced senescence, SIS). Here, we leverage longitudinal and interventional data (Karin et al. 2019; Burd et al. 2013) to test how well a model that includes SIS from long-lived senescent cells captures observed senescent cell dynamics relative to two already published models (Karin et al. 2019). We also estimate an upper bound on the fraction of senescent cells which our models predicts to be long-lived based on longitudinal data.

2 Modeling senescence-induced senescence

As a first step towards building and assessing a model that includes senescence-induced senescence, we re-fit two existing models (Karin et al. 2019) of senescent cell growth on a longitudinal senescent cell dataset initially produced by Burd et al. (2013) and pre-processed (from images) by Karin et al. (2019).

2.1 Introducing SR and USR base models

In their paper, Karin et al. (2019) apply a maximum likelihood framework and parameter grid search to fit 16 ODE-based models of senescent cell growth. Each of their 16 models was derived by selecting a subset of parameters from the following 'full' model of senescent cell growth with time/age,

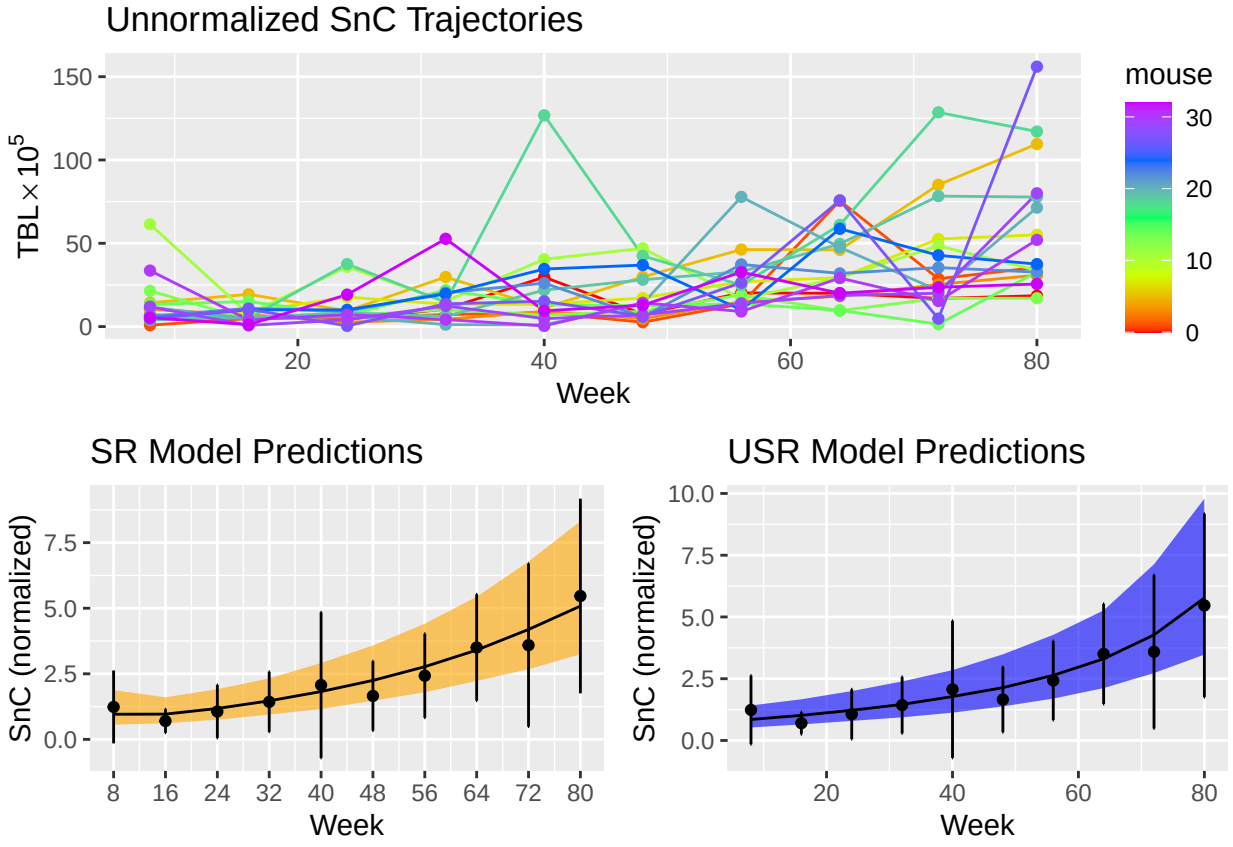
$$\dot{C} = \underbrace{(\eta_0 + \eta_1 * t)(1 + \eta_2 * C)}_{\text{production}} - \underbrace{\frac{\beta_0 - \beta_1 * t}{1 + \beta_2 * C} * C}_{\text{removal}} + \underbrace{\sqrt{2\epsilon} * \xi_t}_{\text{noise}}. \quad (1)$$

In equation (1), C denotes the normalized senescent cell abundance, measured in arbitrary units (AUs) (see Appendix for details). The first of three expression's three variables, η_0, η_1, η_2, denote initial growth rate, growth rate increase with age, and senescence-induced senescence rate respectively. The second of the three expression's three variables, $\beta_0, \beta_1, \beta_2$, denote initial removal rate, decrease in removal rate with age, and inverse of the half-way saturation point for senescent cell removal respectively.

In Karin et al. (2019), the best-performing model variant, the saturated removal (SR) model, got rid of the senescence-induced senescence term but otherwise left the model as-is. The best-performing variant without the saturated removal term (β_2), i.e. the unsaturated removal (USR) model, also excluded the senescence-induced senescence term in its growth rate expression.

2.2 Reproducing the base models in the Bayesian framework

As a baseline for comparing our modified senescence-induced senescence model, we reproduced Karin et al. (2019)'s SR and USR models as Bayesian models in stan (Carpenter et al. 2017) (see Appendix TODO for details on priors, noise model, and stan configuration). At a high level, our results matched theirs. We compared the posterior probability of the two models and found that the SR model was 50.3 times more likely than the USR model (Gronau, Singmann, and Wagenmakers (2020)).



Althought the SR model's full posterior fits the data meaningfully better than the USR model's, as Figure **??** shows, both models' credible intervals and posterior means mostly capture the observed data's evolution through time.

2.2.1 Adding senescence-induced senescence (SIS) to the model

As mentioned, the original full model included a term for SIS. However, the model treated SIS as growing as a function of overall SnC count and total SnC growth rate. Intuitively, given a long enough time this would inevitably lead to exponential growth of the number of senescent cells, which we don't observe. As suggested by Van Deursen (2014), it's instead possible that a small fraction of senescent cells both turn over more slowly and induce senescence in their neighbors, but the majority do not.

To test this hypothesis, we can modify the SR model by replacing the current time-dependent growth rate term with a time-dependent long-lived cell SIS term:

$$\dot{L} = \alpha \tag{2}$$

$$\dot{C} = (\eta_0 + \eta_2 * L) - \frac{\beta_0 - \beta_1 * t}{1 + \beta_2 * C} * C + \sqrt{2\epsilon} * \xi_t. \tag{3}$$

In equation (3), $\dot{L}$ denotes the time rate of change of (latent) long-lived senescent cell count. Solving for L this becomes

$$\dot{C} = (\eta_0 + \eta_2 * c + \eta_2 * \alpha t) - \frac{\beta_0 - \beta_1 * t}{1 + \beta_2 * C} * C + \sqrt{2\epsilon} * \xi_t. \tag{4}$$

where c denotes the long-lived SnC abundance and αt the (assumed to be linear) increase as a function of time.

After fitting this model, we find that it fits the data, as measured by a Bayes Factor, 25 times better (under a uniform prior between models) than the SR model. This suggests that long-lived senescent cell SIS may partially explain senescent cell dynamics when combined with saturated removal.

2.2.2 Validating SIS inferences against literature

To do...

3 Upper bounding the fraction of long-lived SnCs

To do...

4 Limitations

- Can't model spatial dynamics.
- Under-determination issues.
- Strong priors.

5 Appendix

5.1 Differences between our and the original model

5.1.1 Normally-distributed error with ODE vs. stochastic differential equation

5.1.2 Fully Bayesian vs. Maximum Likelihood model

5.1.3 Auto-catalysis term vs. SIS term

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