

# Systems medicine

Uri Alon

## Exercise 3.

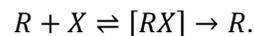
### 6.1. Survival and hazard functions:

- (a) Show that hazard,  $h(\tau)$ , defined as the probability of death per unit time, is related to survival  $S(\tau)$  as follows

$$h(\tau) = -\frac{1}{S} \frac{dS(\tau)}{d\tau} = -\frac{d \log S(\tau)}{d\tau}$$

- (b) Show that  $S(\tau) = e^{-\int h(\tau) d\tau}$
- (c) What is the survival function  $S$  when the hazard follows the Gompertz-law? Plot this survival function.
- (d) What is the survival function if hazard is constant  $h(\tau) = h_0$ ?
- (e) A tree has a hazard function that drops with age,  $h(\tau) = \frac{a}{1+b\tau}$ . What is the survival function? Plot and compare to d and c. What might be a biological cause of such a decreasing hazard function?

**6.2 Removal of SnC based on saturating their own removal process:** SnC are removed by immune cells such as NK cells, which we will denote by  $R$ . There are a total of  $R_T$  removing cells in the body, and that this number does not change appreciably with age (as is indeed the case for NK cells in humans). The  $R$  cells meet SnCs, denoted  $X$ , at rate  $k_{on}$  to form a complex  $[RX]$  which can either fall apart at rate  $k_{off}$ , or end up killing the SnC at rate  $v$ . Thus,



- (a) Explain the following dynamic equation for the complex:

$$\frac{d[RX]}{dt} = k_{on} R X - (v + k_{off}) [RX]$$

- (b) Use the fact that  $R$  cells can be either free or in a complex, so that  $R + [RX] = R_T$ , to show that the removal rate of SnC is

$$removal = \frac{\beta X}{k+X}.$$

- (c) What are the values of the maximal removal capacity  $\beta$ , and the half-way saturation point  $k$  in terms of  $R_T, k_{on}, k_{off}$ , and  $v$ ? Explain intuitively.

**6.3 Age-dependent reduction in repair capacity:** Consider a process in which damage is produced at a constant rate  $\eta$ , and removal does not saturate. Removal rate per cell drops with age,

$$\frac{dX}{dt} = \eta - (\beta - \beta_1\tau)X + \sqrt{2\epsilon}\xi$$

- (a) What is the mean damage  $X$ ?
- (b) What is the distribution  $P(X)$  at age  $\tau$ ?
- (c) What is the ratio of mean and standard deviation of  $X$ :  $\langle X \rangle / \sigma$ ?
- (d) Estimate the hazard, assuming that death occurs when  $X > X_c$ ? Is there a Gompertz law?