LECTURE 3. CELL CYCLE REGULATION

Probabilistic surprises, or not – Noise-driven gain in population growth rate
Let's consider Hashimoto et al's model linking single-cell interdivision times to the population doubling time. The model assumes that each interdivision time is determined by rolling a die (like our bus example from Chapter 1). For the illustrated example, the mean interdivision time is 3.5 h, but the population doubling time is smaller at ≈3.187 h. Let's derive this effect. We proceed by first deriving a relation between interdivision times and the population doubling time, then we use this relation to show that the population doubling time must be smaller than the mean interdivision time.

Suppose interdivision times are drawn independently from a distribution $p(t_d)$. Regardless of the distribution, the number of cells in a population initiated with one cell grows exponentially $N(t) \sim \exp(\Lambda t)$ with some population growth rate Λ. As shown in the illustration, the same population can also be thought of as two sub-populations each initiated by one of the two daughter cells from the first division at time t_1. In this case, the two sub-populations also grow exponentially $N_1(t) \sim \exp\big(\Lambda(t - t_1)\big)$ at the same population growth rate. These two interpretations must be equivalent after averaging over interdivision times, $\exp(\Lambda t) = 2 \int p(t_d) \exp\big(\Lambda(t - t_d)\big) dt_d$. Therefore, we have

$$2 \int \exp(-\Lambda \mathrm{t_d})\, p(t_d) dt_d = 1.$$

This relation is known as the Euler-Lotka equation.

Interestingly, the Euler-Lotka equation suggests that the integrand $q(t_d) = 2\exp(-\Lambda t_d)\, p(t_d)$ is also a probability distribution. Regardless, we can rearrange this expression to obtain

$$\log\left(\frac{p(t_d)}{q(t_d)}\right) = \Lambda t_d - \log 2.$$

We can further rearrange by multiplying both sides by $p(t_d)$ and integrating, which gives

$$D_{\mathrm{KL}}(p|q) = \Lambda \langle t_d \rangle - \log 2,$$

where $D_{\mathrm{KL}}(p|q)$ is the Kullback-Leibler divergence, a metric quantifying the difference between two probability distributions. The KL divergence is an important quantity that we will encounter multiple times. Importantly, it is non-negative:

$$-D_{\mathrm{KL}}(p|q) = \int p(x) \log \frac{q(x)}{p(x)} dx \le \int p(x) \left(\frac{q(x)}{p(x)} - 1\right) dx = 0.$$

The inequality comes from the fact that $\log x \le x - 1$. Therefore,

$$\Lambda \ge \frac{\log 2}{\langle t_d \rangle}.$$

Correlations
Calculate the correlation coefficient in the adder model

$$C(x, y) = \frac{\langle xy \rangle - \langle x \rangle \langle y \rangle}{\sigma_x \sigma_y}$$

Probabilistic surprises, or not – Oscillations vs fluctuations

The autocorrelation function $\rho(\Delta t)$ of a stochastic process is the correlation coefficient C between the values of the process separated by time Δt,

$$\rho(\Delta t) = C(x_t, x_{t+\Delta t}).$$

For the adder model,

$$\rho(\Delta t) = \left(\frac{1}{2}\right)^{\Delta t}.$$

In this case, the autocorrelation function decays exponentially, in agreement with experimental data. Importantly, autocorrelation functions estimated from data are only meaningful after sufficient averaging to eliminate spurious fluctuations.

The difference between oscillations and fluctuations can be differentiated most effectively by computing the power spectrum $S(f)$, which captures the density of the data at different frequencies f. In fact, the power spectrum is the Fourier transform of the autocorrelation function (Wiener-Khinchin theorem). Taking the Fourier transform, we can show that the power spectrum for the adder model has no prominent peaks at any frequency.