# Biophysics Homework II (2021-2022)

ICTP Quantitative Life Sciences Diploma

**Additional theory background: numerical integration of SDEs.** There exist plenty numerical integration techniques of the one-dimensional stochastic differential equation $\mathrm{d}X = f(X,t)\mathrm{d}t + g(X,t)\mathrm{d}B$, whose solution is formally written as

$$X(t) = \int f(X(s), s)\mathrm{d}s + \int g(X(s), s)\mathrm{d}B(s). \tag{1}$$

In the computer, it is only possible to resolve SDEs in discrete time $0, \Delta t, 2\Delta t, ...$, with $\Delta t$ a finite simulation time step. Two commonly used approaches are the following [see e.g. W. Rümelin, SIAM J. Numer. Anal. 19, 604 (1982)].

- Euler scheme: Given $X_t$, the value of the process at $t + \Delta t$ is obtained as follows

  $$X_{t+\Delta t} = X_t + f(X_t, t)\Delta t + g(X_t, t)\Delta B_t, \tag{2}$$

  where $\Delta B_t \sim \mathcal{N}(0, \sqrt{\Delta t})$ is a Gaussian random number with zero mean and standard deviation equal to $\sqrt{\Delta t}$. Note that, to obtain $X_{t+\Delta t}$ in (2) one needs to know: the value of the process in the previous time step $X_t$, the value of the functions $f$ and $g$ evaluated at the previous instances $t$ and $X_t$, and a random number $\Delta B_t$ that is generated anew at each time $t$. This is why this method converges to Eq. (1) when interpreted in the Ito sense.

- Heun scheme: Given $X_t$, the value of the process at $t + \Delta t$ is obtained as follows. First, one computes a prediction of the value in the next time step $\widetilde{X}_{t+\Delta t}$

  $$\widetilde{X}_{t+\Delta t} = X_t + f(X_t, t)\Delta t + g(X_t, t)\Delta \widetilde{B}_t, \tag{3}$$

  with $\Delta \widetilde{B}_t \sim \mathcal{N}(0, \sqrt{\Delta t})$ a Gaussian random number with standard deviation equal to $\sqrt{\Delta t}$. and then one uses both the real previous value $X_t$ and the prediction $\bar{X}_{t+\Delta t}$ to get the value $X_{t+\Delta t}$, as follows:

  $$X_{t+\Delta t} = X_t + \frac{\Delta t}{2}[f(X_t, t) + f(\widetilde{X}_{t+\Delta t}, t + \Delta t)] + \frac{1}{2}[g(X_t, t) + g(\widetilde{X}_{t+\Delta t}, t + \Delta t)]\Delta B_t. \tag{4}$$

  Again here $\Delta B_t \sim \mathcal{N}(0, \sqrt{\Delta t})$ which in each run may be different to $\Delta \widetilde{B}_t$, i.e. one needs to produce two Gaussian random numbers to generate $X_{t+\Delta t}$ from $X_t$. The Heun scheme converges to the Stratonovich solution of Eq. (1) in the limit of $\Delta t$ small.

1. **Active Brownian particles**. The following model has been extensively used to describe the motion of active self-propelled microswimmers (e.g. bacteria, Janus particles, etc.) in two dimensions [C Bechinger et. al, Rev. Mod. Phys. **88** (4) 045006 (2016)]

$$\dot{\theta} = \omega + \sqrt{2D_r}\xi_\theta \tag{5}$$
$$\dot{x} = v\cos(\theta) + \sqrt{2D_t}\xi_x \tag{6}$$
$$\dot{y} = v\sin(\theta) + \sqrt{2D_t}\xi_y. \tag{7}$$

Here, $\omega$ is the average angular velocity of the swimmer, $v$ the self-propulsion speed, $D_r$ the rotational diffusion coefficient, and $D_t$ the translational diffusion coefficient. The three noises are zero-mean Gaussian, white, and independent to each other, each with autocorrelation function $\langle \xi_\theta(t)\xi_\theta(t')\rangle = \langle \xi_x(t)\xi_x(t')\rangle = \langle \xi_y(t)\xi_y(t')\rangle = \delta(t-t')$. For simplicity we may assume $\theta(0) = x(0) = y(0) = 0$.

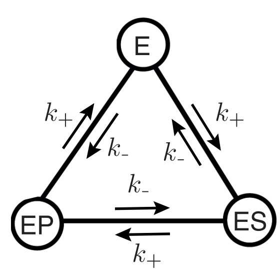
**(a)** Derive an analytical formula for the probability density $P(\theta, t)$.
Does $\theta$ reach a stationary state?
**(b)** Compare the theoretical result obtained in (a) with the probability density of $\theta$ obtained from $10^3$ simulations using the parameter values in (d) for observation times $t = 1, 5,$and 10s.
**(c)** Using stochastic calculus derive a stochastic differential equation for the distance $r(t) = \sqrt{x^2(t) + y^2(t)}$ of the swimmer from the center (both in Ito and Stratonovich). What is the value of $\langle \mathrm{d}r(t)\rangle$ if $D_t = 0$?
**(d)** Consider the parameter values $D_t = 0.2\mu\mathrm{m}^2/\mathrm{s}$, $D_r = 0.17\mathrm{rad}^2/\mathrm{s}$, $v = 30\mu\mathrm{m/s}$, and $\omega = 10\mathrm{rad/s}$. Using Euler's numerical simulation scheme, plot five stochastic trajectories of duration 10s, using a simulation time step $\Delta t = 0.01$s. Repeat the same procedure setting $\omega = 0$ and discuss the obtained result.

2. **Itô's lemma**. Use Itô calculus rules to write the following stochastic processes on the standard form

$$\mathrm{d}X = f(X,t)\mathrm{d}t + g(X,t)\cdot \mathrm{d}B, \tag{8}$$

i.e. find the functions $f(X,t)$ and $g(X,t)$, for:
**(a)** $X = B^2$.
**(b)** $X = A\cos(\omega t + B)$.
**(c)** $X = B/(1 + t/\tau)$.
**(d)** $X = e^{-B^2/2t}$.

3. **Statistics of enzymatic reactions**. Consider a three-state continuous-time Markov jump model of the cyclic enzymatic reaction illustrated in the figure




Here the circles denote the three different states of the enzyme (E: free enzyme; ES: enzyme bound to substrate; EP: enzyme bound to product), and $k_+$ and $k_-$ are respectively the clockwise and counterclockwise transition rate in the state space.

**(a)** Write down the Master equation associated with the dynamics of the enzyme, both as a system of equations and also in its matrix form $\mathrm{d}\vec{P}/\mathrm{d}t = \mathbf{W}\vec{P}$, with $\vec{P}$ a probability column vector.
**(b)** Compute the eigenvalues and eigenvectors of the transition matrix $\mathbf{W}$.
Hint: find and use the known expressions for the eigenvalues/vectors of a circulant matrix.
**(c)** Calculate the stationary distribution and stationary current of the system, and the characteristic relaxation times of a system that is initially out of steady state.
Hint: the relaxation times can be found from the eigenvalue spectrum of $\mathbf{W}$.
**(d)** Evaluate, with the help of a computer, the value of the three components of the probability vector $\vec{P}(t)$ describing the probability of an ensemble of enzymes to be in any of the three possible states. Assume that the enzymes are initially free, i.e. at time $t = 0$ the system is in state E with probability one. Compare the results of two different methods: (i) numerical integration of the system of ordinary differential equations given by the Master equation; (ii) performing the average over many (at least $10^3$) stochastic trajectories obtained using the Gillespie algorithm. Plot few trajectories obtained from the Gillespie algorithm method.
Values of the parameters $k_+ = 10\mathrm{Hz}$, $k_- = 1\mathrm{Hz}$, total integration time $t_{\max} = 3\mathrm{s}$.

4. **Four-state model of molecular motor**. Experimentalists sketched a Markov jump model of molecular motor stepping:

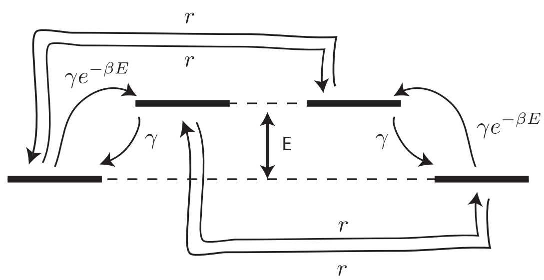



Figure 1: Sketch of the model.

Here, $r$ and $\gamma$ are two rate parameters, $\beta = 1/k_{\mathrm{B}}T$ and $E$ is the energy difference between two adjacent energy levels, and $T$ is the temperature of the environment.
**(a)** Write the Master equation of the model in matrix form.
**(b)** Calculate the probability to be in any of the state in the long time limit, i.e. its stationary value. Compare this result with the associated Boltzmann distribution.
**(c)** What is the stationary current between each of the states? Sketch the direction of the current between all the states. For which value of $E$ is the current equal to zero?

5. The dynamics of a photoreceptor neuron subject to a light source of frequency $\omega$ can be modelled as a two-state continuous-time Markov process with *time-dependent* transition rates

$$\omega_{21}(t) = \mu \cos^2(\omega t), \tag{9}$$
$$\omega_{12}(t) = \mu \sin^2(\omega t), \tag{10}$$

where $\mu > 0$ is a characteristic rate parameter.
**(a)** Plot the transition rates as a function of time, for a given value of $\omega$. What happens if the frequency of the incident light is doubled?
**(b)** Write the Master equation describing the dynamics of the probabilities $P_1(t)$ and $P_2(t)$ for the neuron to be at state 1 and 2 at time $t$, respectively.
**(c)** Derive analytical expressions for $P_1(t)$ and $P_2(t)$.
**(d)** Evaluate $P_1(t)$ and $P_2(t)$ in the limit of $t$ large, i.e. when $t \gg \mu^{-1}$.

**Deadline**: 7th January, 2021.