IMPERIAL

MATH70137

BSc, MSci and MSc EXAMINATIONS (MATHEMATICS)
May 2024

This paper is also taken for the relevant examination for the
Associateship of the Royal College of Science

Mathematical Biology 2: Systems Biology

Date: Wednesday, May 29, 2024

Time: 10:00 – 12:30 (BST)

Time Allowed: 2.5 hours

This paper has 5 Questions.

Please Answer All Questions in 1 Answer Booklet

Candidates should start their solutions to each question on a new sheet of paper.

Supplementary books may only be used after the relevant main book(s) are full.

Any required additional material(s) will be provided.

Allow margins for marking.

Credit will be given for all questions attempted.

Each question carries equal weight.

DO NOT OPEN THIS PAPER UNTIL THE INVIGILATOR TELLS YOU TO

© 2024 Imperial College London

1. In this question, we will consider the strategies that bacteria may employ to deal with toxin molecules that are byproducts of their activities. Let x denote the concentration of a specific toxin molecule in a growing population of bacteria.

(a) Consider the following ODE for the dynamics of x:

$$\dot{x} = \alpha - \gamma(x)x \tag{1}$$

with:

$$\gamma(x) = \gamma_0 \frac{K^n}{K^n + x^n} \tag{2}$$

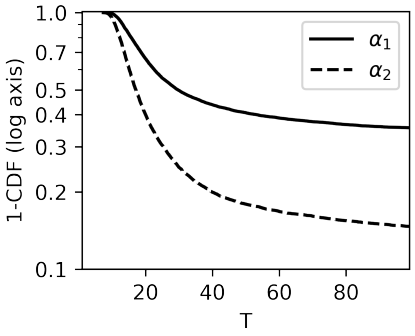
where K, γ_0 are positive numbers and $n \geq 2, \alpha \geq 0$. Provide an interpretation of Eqs. (1) and (2) in terms of the effect of x on the growth rate of the bacteria. (2 marks)

(b) Analyze the dynamics of x as a function of α. Specifically, describe the number and stability of the fixed points for different values of α and calculate critical values of α, x. (6 marks)

(c) Draw a bifurcation diagram of x as a function of α, and label the critical values of x and α. (4 marks)

(d) In standard growth conditions bacteria segregate all molecules evenly between their daughter cells. Experimentalists working on E. coli discovered that when they are grown in stressful environments that are associated with a high toxin production rate, they perform asymmetric segregation of toxin molecules such that one of the daughter cells receives most of the toxin molecules. Using your analysis, explain, in no more than a few sentences, why a conditional transition to aging may be beneficial for the bacteria. Refer to the bifurcation diagram in your answer. (4 marks).

(e) Assume that bacteria decide to transition to asymmetric segregation of x when the level of x exceeds a threshold x_Ω. Consider experiments where α is increased from $\alpha = 0$ to a higher level $\alpha = \alpha_1$ or $\alpha = \alpha_2$, where $\alpha_1 < \alpha_2$. In these experiments, the time until individual bacteria in a population transition to asymmetric segregation (T) after the step change has been measured, with the $(1 - CDF(T))$ (where CDF is the cumulative density function) plotted below. Provide a short interpretation of the results.



(4 marks)

(Total: 20 marks)

2. The thyroid axis is a neuroendocrine axis that controls the metabolic activity of the body. It consists of the following hormones: TRH (x_1) is secreted from the hypothalamus and causes TSH to be secreted from the pituitary gland. TSH (x_2) causes the secretion of thyroid hormones (x_3) from the thyroid gland, which, in turn, inhibits both TSH and TRH secretion. Consider the following model for the thyroid axis:

$$\begin{aligned} \dot{x_1} &= \frac{u}{x_3} - \beta x_1 \\ \dot{x_2} &= P\frac{x_1}{x_3} - x_2 \\ \dot{x_3} &= Tx_2 - x_3 \end{aligned} \tag{1}$$

where u is the input to the system, P is the effective mass of the pituitary gland, T is the mass of the thyroid gland, and $\beta \gg 1$, so the dynamics of x_1 are much faster than x_2 and x_3. The dynamics of x_2, x_3 are on the order of hours.

(a) Obtain the fixed point of the system, fixing u. Analyze the stability of this fixed point, using the assumption that the dynamics of x_1 adjust much faster than x_2, x_3.

(5 marks)

(b) Consider now a modification to the model, where the following two equations are added:

$$\begin{aligned} \dot{P} &= \alpha_1 P(c_3 - x_3) \\ \dot{T} &= \alpha_2 T(x_2 - c_2) \end{aligned} \tag{2}$$

where $\alpha_1, \alpha_2, c_1, c_2$ are positive constants. Interpret the biological meaning of Eq. 2.

(2 marks).

(c) What is the steady state of the new model? (You do not need to analyze its stability, and can assume it is stable).

(3 marks)

(d) In the modified model, consider the dynamics of the system from steady-state following a prolonged constant input $u = \lambda u_0$. Show that the dynamics of x_2 or x_3 in response to some (arbitrary) input $\lambda u(t)$ ($\lambda > 0$) are independent of λ.

(4 marks)

(e) Iodine is required for the synthesis of thyroid hormone (x_3). Prior to the addition of iodine to table salt, people with iodine-deficient diets tended to develop thyroid goiters, which are a pathological overgrowth of the thyroid glands. Use your model to explain this, assuming that iodine deficiency results in a multiplicative decrease in the production rate of x_3.

(4 marks)

(f) Researchers identified oscillatory dynamics in the pituitary, where the parathyroid and thyroid glands appear to be anti-correlated and oscillate with irregular amplitude and a period of several months. What may be the source of these oscillations? Using the modified model, provide a short reasoning (there is no need for a quantitative solution).

(2 marks)

(Total: 20 marks)

3. Here you will study the remarkable thermal sensing capabilities of pit vipers. Pit vipers can sense very small changes in the temperature of an object compared with the background temperature using a specialized thermal imaging organ called the pit organ. The pit organ senses temperature by adjusting the firing rate of temperature-dependent ion channels. The firing rate is given by:

$$p(V,T,K) = \frac{V^n}{K^n T^{-n} + V^n} \tag{1}$$

where T is the temperature, K is a constant, and V is a dynamic variable corresponding to the voltage of the nerve ending, and $n \gg 1$, so p is step-like. Let C be a small positive constant. The dynamics of V are:

$$\dot{V} = p(V,T,K) - (V - C) \tag{2}$$

(a) Using graphical arguments, identify the dynamical regimes of the system, fixing T and adjusting K from $K \approx 0$ to $K \to \infty$. Label the critical K values. (5 marks)

(b) Consider dynamics starting from $V = 0$ at a sustained, fixed temperature T. After the system had stabilized, there is a slight increase in the temperature $T \to T + \delta T$. For which values of K is the effect of the step increase in T on the firing rate $p(V,T,K)$ most pronounced? (3 marks)

(c) Consider now modified dynamics of V where there is multiplicative white noise:

$$dV = (p(V,T,K) - (V - C))\,dt + \sigma V\,dW \tag{3}$$

where σV is small in the relevant dynamical region and W is the noise process. How does this noise term affect your answer to (2)? Answer in one sentence. (1 mark)

(d) Firing occurs with stochastic reset, that is, when the nerve ending is firing at $p \approx 1$ there is a stochastic reset of V to $V \approx 0$ with some probability λ. Provide a short qualitative description of the dynamics of p when K is near the sensitive regime from (c). (3 marks)

(e) Consider now that there are N nerve ends (N is very large), so now the dynamics of each nerve end is given by:

$$dV_i = (p(V_i,T,K) - (V_i - C))\,dt + \sigma V_i\,dW_i \tag{4}$$

and that the nerve ends are coupled by the parameter K, which is controlled by negative feedback from the firing neurons:

$$K = \alpha \sum_{i=1}^{N} \theta(i) \tag{5}$$

where $\theta(i) = 1$ if $p(V_i,T,K) \approx 1$, and otherwise $\theta(i) = 0$. Identify an analytical criterion on α so that the system settles near a regime where it is most sensitive to changes in T (use the provided constants and/or critical K values). (6 marks)

(f) What is the long-term effect of a change in the temperature T on the firing properties of the population in the self-tuning regime? (2 marks)

(Total: 20 marks)

4. Consider the standard Wright-Fisher (WF) model as studied in class (haploid, no selection, no mutation), with a fixed population size N, focusing on a gene that has two alleles A and a. Initially, there are i copies of allele A and $N-i$ copies allele a in the population. Let $p_0 = i/N$ denote the initial fraction of individuals that carry allele A.

   For the WF model, time proceeds in discrete steps, $t = 0, 1, 2, ...$, and at every step all the individuals in the system are replaced by N offspring, sampled with replacement from the current population.

   (a) Denote by P_t the random variable representing the fraction of individuals that carry allele A at the t-th time-step. Show that:

   $$\mathbb{E}[P_1] = p_0, \qquad \mathsf{Var}[P_1] = \frac{p_0(1-p_0)}{N}. \tag{1}$$

   . (2 marks)

   (b) The heterozygosity H of a population is defined as the probability that, sampling two individuals with replacement, they carry two different alleles. Calculate H_0^{WF}, the heterozygosity at $t = 0$ in the Wright-Fisher model. (2 marks)

   (c) Using the results in Eq. (1), show that, for $\mathbb{E}[H_1^{WF}]$, the expected heterozygosity at $t = 1$, you have:

   $$\mathbb{E}[H_1^{WF}] = H_0^{WF}\left(1 - \frac{1}{N}\right) \tag{2}$$

   (2 marks)

   (d) Keeping in mind Eq. (2) and that $\mathbb{E}[H_t^{WF}] = \mathbb{E}[H_{t-1}^{WF}]\left(1 - \frac{1}{N}\right)$ (proof not required), show that:

   $$\mathbb{E}[H_t^{WF}] = H_0^{WF}\left(1 - \frac{1}{N}\right)^t. \tag{3}$$

   (2 marks)

   Now consider the standard Moran process as studied in class (haploid, no selection, no mutation), with a fixed population size N, Focusing on a gene that has two alleles A and a. Initially, there are i copies of allele A and $N-i$ copies allele a in the population. Let $p_0 = i/N$ denote the initial fraction of individuals that carry allele A.

   In the Moran process, time proceeds in discrete steps, $\tau = 0, 1, 2, ...$, and at every time step, two individuals are selected at random, with replacement. One individual is removed from the population, while the other copies itself (note that the two individuals chosen may be the same). Each individual has the same probability of being selected in each draw.

   (e) Denote by P_τ the random variable representing the fraction of individuals that carry allele A at time τ. Show that, for the Moran model:

   $$\mathbb{E}[P_1] = p_0, \qquad \mathsf{Var}[P_1] = \frac{2p_0(1-p_0)}{N^2}. \tag{4}$$

   (2 marks)

(f) Consider heterozygosity in the Moran model, H^M, defined as in the Wright-Fisher model. Show that:

$$\mathbb{E}[H_1^M] = H_0^M \left(1 - \frac{2}{N^2}\right) \tag{5}$$

(2 marks)

(g) Using that $\mathbb{E}[H_\tau^M] = \mathbb{E}[H_{\tau-1}^M]\left(1 - \frac{2}{N^2}\right)$ (proof not required) and Eq. (5), show that

$$\mathbb{E}[H_\tau^M] = H_0^M \left(1 - \frac{2}{N^2}\right)^\tau \tag{6}$$

(2 marks)

(h) In the large population size limit, $N \gg 1$, calculate the half-lives of the heterozygosities in the two models. (4 marks)

(i) The two half-lives are not directly comparable, because of the different meaning of a time step and of the time variables t and τ in the two models. Calculate the expected lifetime of an individual in the Moran model (motivating your calculation), and re-scale time in the Moran model counting it in units of this average lifetime. Reconsidering the two half-lives after re-scaling time in the Moran model, explain the statement: "The rate of genetic drift in the Moran model is twice as fast as that in the Wright-Fisher model. " (2 marks)

(Total: 20 marks)

5. A classical Hopfield network is a feedback network where pairwise interactions define dynamics that can converge to specific attractors. Here you will consider a generalization of this concept by Krotov and Hopfield (2016) to higher-order interactions.

The state of this network is given by a vector $x \in \{-1, 1\}^N$. Consider a set of K memories $\xi^1, \ldots, \xi^K$, each also a vector of length N, $\xi^\mu \in \{-1, 1\}^N$:

$$\xi^\mu = (\xi_1^\mu, \ldots, \xi_K^\mu) \tag{1}$$

Recall that for a classical Hopfield network, the weight matrix w is given by:

$$w_{i,j} = \sum_{\mu=1}^{K} \xi_i^\mu \xi_j^\mu \tag{2}$$

There is also an update rule that is associated with an energy function:

$$E_{\text{classical}}(x) = -\sum_{i=1}^{N}\sum_{j=1}^{N} x_i w_{i,j} x_j \tag{3}$$

Here, in contrast, we will consider an update rule that is associated with an energy function:

$$E(x) = -\sum_{\mu=1}^{K} F\left(\sum_{i=1}^{N} \xi_i^\mu x_i\right) \tag{4}$$

Where $F(z) = z^n$ for some $n \geq 2$. In general, both $N, K \gg 1$.

(a) Prove that the new energy function E is equivalent to the classical Hopfield energy function $E_{\text{classical}}$ for $n = 2$.

(4 marks)

(b) Consider the following asynchronous update rule, for each $i \in 1 \ldots N$:

$$x_i(t+1) \leftarrow \text{sign}\left[\sum_{\mu=1}^{K} F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right)\right] \tag{5}$$

Show that, for $n \geq 2$, the dynamics with the update rule from some initial state converges to a local minimum of $E(x)$ or a limit cycle where $E(x)$ is constant.

(8 marks)

(c) Now, assuming that the bits of the patterns are all statistically independent and take the values $-1, 1$ with equal probability, show that:

$$\mathbb{E}\left[E(\xi^\mu) - E(\hat{\xi^\mu})\right] = (N-2)^n - N^n \tag{6}$$

where $\hat{\xi^\mu}$ is identical to ξ^μ in all but a single corrupted bit (flipped from 1 to -1 or -1 to 1).

(6 marks)

(d) How would changing the number of stored patterns K affect the stability of the memory patterns? Give a short, qualitative answer, referring to your calculation in (c).

(2 marks)

(Total: 20 marks)

Mathematical Biology 2 (Spring 2024): Exam Solutions

Omer Karin

Problem 1. Solution:

(a) x inhibits the growth of the bacteria.

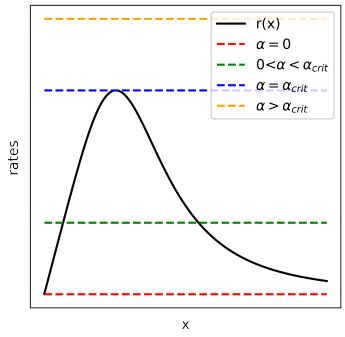
(b) Consider the overall removal rate $r(x) = \gamma(x)x = \gamma_0 \frac{xK^n}{K^n+x^n}$. We have that $r(0) = 0$ and $r(x \to \infty) = 0$. The function has a single maximum at $x_{\text{crit}} = \frac{K}{\sqrt[n]{n-1}}$:

$$\frac{\partial r}{\partial x} = x\gamma'(x) + \gamma(x) = \gamma_0 \frac{K^n \left(K^n - (n-1)x^n\right)}{\left(K^n + x^n\right)^2} = 0$$

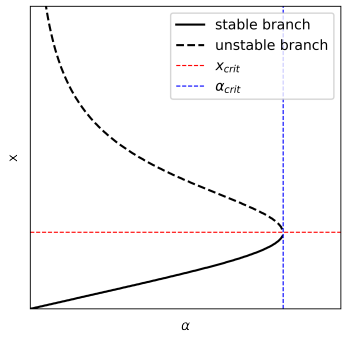
where:

$$\alpha_{\text{crit}} = r(x_{\text{max}}) = \gamma_0 \frac{K(n-1)^{1-\frac{1}{n}}}{n}$$

thus, for $\alpha = 0$ there will be a single stable fixed point at $x = 0$. For $0 < \alpha < \alpha_{\text{crit}}$ there will be two fixed points, a lower stable fixed point and a higher unstable one, which will coalesce to a single semi-stable fixed point at α_{crit} where $x = x_{\text{crit}}$. Finally, the dynamics diverge to infinity at $\alpha > \alpha_{\text{crit}}$.



(c) The bifurcation diagram:



(d) When production exceeds the critical α_{crit} with symmetric partitioning, the toxins diverge towards high x where growth is inhibited. Thus, there is no long-term exponential growth with symmetric partitioning for $\alpha > \alpha_{\text{crit}}$. On the other hand, when partitioning is asymmetric, some lineages will accumulate x at faster rate (twice as fast at the most extreme), but for some lineages, damage accumulation will be much lower (with $\alpha = 0$ at the most extreme), allowing for exponential growth.

(e) For large values of α near the critical transition ($\alpha \approx \alpha_{\text{crit}}$), the delay to asymmetric segregation will be dominated by the delay near x_{crit}. There, slight variations in biochemical parameters between individual bacteria are amplified, with some bacteria in the monostable regime and others in the bistable regime, resulting in a heavy-tailed survival distribution. Slight variation in α_1, α_2 results in different proportions of the bacteria in the monostable and bistable regimes.

Note: Graphical analysis and bifurcation diagram are similar to problems presented in class, e.g. for the Diabetes model. (d) Requires only some rather straightforward reasoning about the underlying biology captured by the model. (e) Is similar to the analysis of variation by a saddle-node bifurcation seen in class.

Problem 2. Solution:

(a) The fixed point is at:

$$x_1 = \left(\frac{u^2}{\beta^2 PT}\right)^{1/3},\ x_2 = \left(\frac{Pu}{\beta T^2}\right)^{1/3},\ x_3 = \left(\frac{PTu}{\beta}\right)^{1/3}$$

Taking a quasi-steady-state on x_1, we can analyze the dynamics of the feedback between x_2, x_3. The quasi-steady-state is $x_1 = \frac{u}{\beta x_3}$, and the reduced, two-dimensional dynamics, are given by:

$$\dot{x_2} = P\frac{u}{\beta x_3^2} - x_2$$
$$\dot{x_3} = Tx_2 - x_3$$

The Jacobian, evaluated at the steady-state, is:

$$J = \begin{pmatrix} -1 & -\frac{2}{T} \\ T & -1 \end{pmatrix}$$

with the eigenvalues $\lambda_{1,2} = -1 \pm \sqrt{2}i$. The dynamics of the fixed point are thus damped oscillatory.

(b) Thyroid hormones inhibit the growth rate of the cells of the pituitary gland and TSH stimulates the growth of the cells of the thyroid gland.

(c) Now, at steady-state, $x_2 = c_2, x_3 = c_3$ and $x_1 = \frac{u}{\beta c_3}$. The steady-state gland masses are $P = \frac{\beta c_2 c_3^2}{u}$ and $T = \frac{c_3}{c_2}$.

(d) The dynamics of x_2, x_3 from steady-state are invariant to the input scale. To see this, consider a general input $\lambda u(t)$ where $\lambda > 0$. We relabel $\hat{x_1} = \lambda^{-1} x_1$ and $\hat{P} = \lambda P$. At steady state, we have that $\hat{x_1} = \lambda^{-1} x_1 = \frac{u}{\beta c_3}$ and $\hat{P} = \lambda P = \frac{\beta c_2 c_3^2}{u}$. The dynamics are:

$$\dot{\hat{x_1}} = \lambda^{-1}\dot{x_1} = \frac{u}{x_3} - \lambda^{-1}x_1 = \frac{u}{x_3} - \hat{x_1}$$
$$\dot{x_2} = \lambda P\frac{\lambda^{-1}x_1}{x_3} - x_2 = \hat{P}\frac{\hat{x_1}}{x_3} - x_2$$
$$\dot{x_3} = Tx_2 - x_3$$
$$\dot{\hat{P}} = \lambda\hat{P} = \alpha_1\lambda P(c_3 - x_3) = \alpha_1\hat{P}(c_3 - x_3)$$
$$\dot{T} = \alpha_2 T(x_2 - c_2)$$

Which are invariant of λ.

(e) To see this, consider the modification of the dynamics of x_3 to consider iodine production in iodine-deficient diets, where the production is reduced:

$$\dot{x_3} = \epsilon Tx_2 - x_3$$

with $\epsilon \approx 0$. Now, at steady-state, $x_2 = c_2$ and $x_3 = c_3$, so now we must have that in the pathological steady-state, $T_{\text{path}} = \frac{c_3}{c_2\epsilon}$ compared with the healthy steady-state $T_{\text{healthy}} = \frac{c_3}{c_2}$, so:

$$\frac{T_{\text{path}}}{T_{\text{healthy}}} = \epsilon^{-1}$$

which corresponds to a greatly enlarged thyroid in the pathological condition.

(f) Oscillations with irregular amplitude correspond to noise-induced oscillations, and they can occur in 2-component negative feedback circuits. Since the hormones have a timescale of hours, the oscillations may be due to the dynamics of the glands.

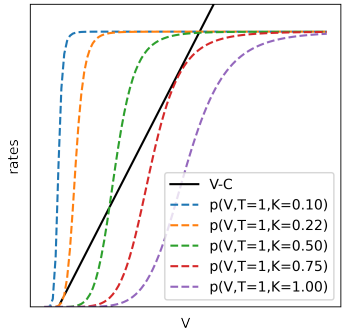
Note: (a) is similar to many analysis seen in class and in the worksheet. (b,c) are related to the Diabetes model. (d) Is similar to the analysis in the Diabetes model and Incoherent Feedforward as well as coursework, but slightly more complicated. (e) Is more difficult as it requires reasoning and understanding of the model. (f) Noise-induced oscillations were analyzed in class and in the worksheet.

Problem 3. Solution:

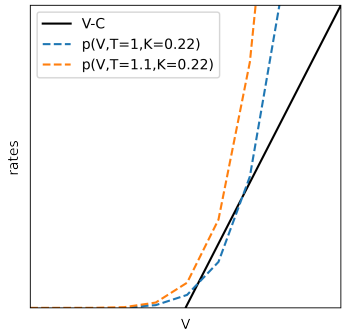
(a) The dynamics are given by:

$$\dot{V} = \frac{V^n}{K^n T^{-n} + V^n} - (V - C)$$

When K is very small there is a single stable fixed point at $p \approx 1$. When it is very large, there is a single stable fixed point at $p \approx 0$. When it is intermediate $\kappa_1 T < K < \kappa_2 T$, the system is bistable at $p \approx 1$ and $p \approx 0$ with an unstable fixed point at an intermediate p corresponding to $V \approx K$. At the critical $\kappa_1 T, \kappa_2 T$ there are saddle-node bifurcations.



(b) A slight increase in the temperature T decreases K slightly. When the system is in the regime where $K = \kappa_1 T + \epsilon$ with (ϵ a small number), under the conditions described in the question, the system will be at a stable fixed point where $p \approx 0$. A slight increase in T can then transition the system to a monostable regime, leading to a transition to $p \approx 1$. This is, therefore, the regime where the system is most sensitive to step increases in T.



(c) When noise is small the sensitivity to δT is still the largest in this critical region of $K \approx \kappa_1 T$.

(d) When K is critical, trajectories have a prolonged delay around the critical point where $p \approx 0$, followed by a rapid transition to $p = 1$, and then a stochastic reset at rate λ.

(e) When K is very small the transition time from $p \approx 0$ to $p \approx 1$ is of order unity. Let z denote the fraction of neuron ends firing ($p \approx 1$) at the stationary state. If the system is settled around the critical regime, then:

$$K = \alpha N z \approx \kappa_1 T$$

that is:

$$Nz = \frac{\kappa_1 T}{\alpha}$$

so:

$$z = \frac{\kappa_1 T}{\alpha N}$$

Denoting by τ the steady-state delay in the transition from $p \approx 0$ to $p \approx 1$, we also have that at steady-state, the delay τ is equal to the ratio of neuron ends at $p \approx 0$ (given by $N(1-z)$) to the arrival rate at $p \approx 0$ (given by $\lambda N z$):

$$\tau = \frac{N(1-z)}{\lambda N z} = \frac{1}{\lambda}\left(\frac{1}{z} - 1\right) = \frac{1}{\lambda}\left(\frac{\alpha N}{\kappa_1 T} - 1\right)$$

Since the system settles at the critical regime when $\tau > 1$, we require that:

$$\alpha > N^{-1}(\lambda + 1)\kappa_1 T$$

(f) The average firing rate z increases with T:

$$z = \frac{\kappa_1 T}{\alpha N}$$

Note: (a) requires graphical analysis with a similar exercise provided in the worksheet. (b) is similar to worksheet exercise and requires reasoning about saddle-node bifurcation. (c,d) straightforward from lectures, (e) more challenging but similar to lecture notes and exercise, (f) should be straightforward upon success in (e).

Problem 4. Solution:

(a) Denote by j the number of copies of allele A at $t = 1$. The random variable j follows a binomial distribution with parameters N and $p_0 = i/N$. Therefore, the expected values of the number if copies is $Np_0 = i$, the variance is $Np_0(1 - p_0)$ (seen in class). For the fraction of the number of copies, namely for $P_1 = j/N$, we have

$$E[P_1] = E\left[\frac{i}{N}\right] = \frac{E[i]}{N} = \frac{Np}{N} = p, \qquad V[P_1] = V\left[\frac{i}{N}\right] = \frac{V[i]}{N^2} = \frac{Np(1-p)}{N^2} = \frac{p(1-p)}{N} \tag{1}$$

Note: this is basic material covered in the lecture notes; similar question asked in a problem set.

(b) $H_0^{WF} = 2p_0(1 - p_0)$. This is the probability of drawing one copy of allele A and one of allele a when drawing two copies at random with replacement, if the fraction of copies of A is p_0. This can be also seen as a binomial experiment, with two trials ($N = 2$) with success probability $p = p_0$, with $2p_0(1 - p_0)$ being the probability of one success and one failure (in any order).

Note: this is basic material covered in the lecture notes; similar question asked in a problem set.

(c) From the definition of heterozigosity, for any time step we have $H_t = 2P_t(1 - P_t)$. Focussing on $t = 1$:

$$\begin{aligned} E[H_1] &= E[2P_1(1 - P_1)] = 2E[P_1 - P_1^2] \\ &= 2(E[P_1] - E[P_1^2]) = 2(E[P_1] - E[P_1]^2 - V[P_1]), \end{aligned} \tag{2}$$

where we used the linearity of expectation, and the last equality comes from the property of the variance $V[X] = E[X^2] - E[X]^2$. Now, knowing that in the Wright-Fisher model $E[P_1] = P_0$ and $V[P_1] = P_0(1-P_0)/N$:

$$\begin{aligned} E[H_1^{WF}] &= 2(P_0 - P_0^2 - \frac{P_0(1 - P_0)}{N} \\ &= 2\left[P_0(1 - P_0) - \frac{P_0(1 - P_0)}{N}\right] \\ &= 2P_0(1 - P_0)\left(1 - \frac{1}{N}\right) = H_0^{WF}\left(1 - \frac{1}{N}\right). \end{aligned} \tag{3}$$

Note: Slightly more advanced material, but derivation sketched in lecture notes and similar question (with full derivation required) asked in a problem set.

(d) Use the given recurrence relation between expected values to express $E[H_t^{WF}]$ in terms of $E[H_1^{WF}]$. The final relationship is then obtained expressing $E[H_1^{WF}]$ in terms of H_0^{WF}, using the result of the previous point.

(e) The expected value and variance of j can be derived by direct calculation from the $\Pr(j|i)$ given in the problem, and then the results for the fraction P_1 can be obtained as done in point 1.

Note: this is basic material covered in the lecture notes; similar question asked in a problem set.

(f) Very similar to (c). The difference lies in the expression for the variance of P_1 in the Wright-Fisher and Moran model, which causes the term $1/N$ to be replaced by $2/N^2$.

Note: Slightly more advanced material. Heterozygosity in Moran model was not discussed in lectures or notes, therefore requires some level of independence and critical thinking. However, calculations are analogous. Therefore a bit more challenging.

(g) Same as (d).

(h) For large N, the decay of heterozygosity can be approximated as exponential.

In Wright-Fisher:

$$E[H_t^{WF}] \approx H_0^{WF} e^{-t/N}. \tag{4}$$

In Moran model:

$$E[H_\tau^{M}] \approx H_0^{M} e^{-2\tau/N^2}. \tag{5}$$

For half-lives, we have respectively for Wright-Fisher and Moran

$$t_{1/2} = N \ln 2, \qquad \tau_{1/2} = \frac{N^2}{2} \ln 2 \tag{6}$$

Note: The exponential approximation (not half-life) for Wright-Fisher decay of heterozygosity was asked in a problem set.

(i) The lifetime of an individual in the Moran model follows a geometric distribution with probability of success (death) $1/N$. The expected value is therefore N. Re-defining moran time as $\tau^* = \tau/N$, we have that the half-life of heterozygosity in Moran is:

$$\tau^*_{1/2} = \frac{N}{2} \ln 2, \tag{7}$$

namely half of the half-life in Wright-Fisher model.

The two time variables are now comparable, because the average lifetime of an individual in Moran model can be seen as a generation in the population, and a time step in Wright-Fisher is indeed a full generation.

The decay of heterozygosity H in the two basic models without no selection or mutation is entirely due to random genetic drift. Indeed, the rate of decay of heterozygosity is identified as the rate of random genetic drift. As the life-time of H in the Moran model is half of that in the Wright-Fisher model, the decay of heterozygosity is twice as fast in the Moran model.

The candidate might have found this relationship reasoning on the exponential decays directly, without calculating the half-lives (previous points).

Note: One problem sheet has a question about the distribution of lifetime of an individual in Moran model, but this was not taken to calculation of the mean and re-scaling.

Note: The last points are more advanced. They require some independent thinking, understanding of the relation between random genetic drift and the decay of heterozygosity, having solved and understood (and remembering) the problem sheets.

Problem 5. Solution:

(a) The classical energy function is:

$$E_{\text{classical}}(x) = -\sum_{i=1}^{N}\sum_{j=1}^{N} x_i w_{i,j} x_j = -\sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{\mu=1}^{K} x_i x_j \xi_i^\mu \xi_j^\mu$$

The revised energy function, for $n = 2$:

$$\begin{aligned}
E(x) &= -\sum_{\mu=1}^{K} F\left(\sum_{i=1}^{N} \xi_i^\mu x_i\right) \\
&= -\sum_{\mu=1}^{K} \left(\sum_{i=1}^{N} \xi_i^\mu x_i\right)^2 \\
&= -\sum_{\mu=1}^{K}\sum_{i=1}^{N} \xi_i^\mu x_i \left(\sum_{j=1}^{N} \xi_j^\mu x_j\right) \\
&= -\sum_{\mu=1}^{K}\sum_{i=1}^{N}\sum_{j=1}^{N} \xi_i^\mu x_i \xi_j^\mu x_j \\
&= -\sum_{i=1}^{N}\sum_{j=1}^{N}\sum_{\mu=1}^{K} x_i x_j \xi_i^\mu \xi_j^\mu \\
&= E_{\text{classical}}(x)
\end{aligned}$$

(b) For the update rule:

$$x_i(t+1) \leftarrow \text{sign}\left[\sum_{\mu=1}^{K} F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right)\right] \tag{8}$$

Consider an update round for bit i. If bit i did not flip then the energy did not change. Otherwise we will mark $x(t) = x$ and note that $x_i(t+1) = -x_i$. Thus:

$$x_i \leftarrow \text{sign}\left[\sum_{\mu=1}^{K} F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right)\right] \tag{9}$$

consider the energy difference:

$$E(x(t+1)) - E(x(t)) = \sum_{\mu=1}^{K} F\left(x_i \xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - \sum_{\mu=1}^{K} F\left(-x_i \xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) \tag{10}$$

Now, if $x_i = 1$ then by Eq. 9 :

$$\sum_{\mu=1}^{K} F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) > 0$$

so:

$$E(x(t+1)) - E(x(t)) = \sum_{\mu=1}^{K} F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - \sum_{\mu=1}^{K} F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) < 0 \tag{11}$$

on the other hand, if $x_i = -1$, then again by Eq. 9:

$$\sum_{\mu=1}^{K} F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) < 0$$

so:

$$E(x(t+1)) - E(x(t)) = \sum_{\mu=1}^{K} F\left(-\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) - \sum_{\mu=1}^{K} F\left(\xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu x_j\right) < 0 \tag{12}$$

Thus, the energy (weakly) decreases along the dynamics. Note that the energy is bounded from below as x and $\xi^1, \ldots, \xi^K$ are all bounded from below and above. Thus, the dynamics are associated with a bounded energy function that decreases along trajectories, and thus they will converge to a stable fixed point or limit cycle.

(c) Let us assume, without loss of generality, that $\xi_i^\mu = 1$ and it is corrupted to $\hat{\xi_i^\mu} = -1$. Then:

$$\begin{aligned}
E(\xi_i^\mu) - E(\hat{\xi_i^\mu}) &= \sum_{\nu=1}^{K} F\left(-\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right) - \sum_{\nu=1}^{K} F\left(\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right) \\
&= F\left(-\xi_i^\mu \xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\mu\right) - F\left(-\xi_i^\mu \xi_i^\mu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\mu\right) \\
&+ \sum_{\nu\neq\mu} F\left(-\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right) - F\left(\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right) \\
&= (N-2)^n - N^n \\
&+ \sum_{\nu\neq\mu} F\left(-\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right) - \sum_{\nu\neq\mu} F\left(\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right)
\end{aligned} \tag{13}$$

Now:

$$\begin{aligned}
\mathbb{E}\left[E(\xi^\mu) - E(\hat{\xi^\mu})\right] &= (N-2)^n - N^n \\
&+ \mathbb{E}\left[\sum_{\nu\neq\mu} F\left(-\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right)\right] - \mathbb{E}\left[\sum_{\nu\neq\mu} F\left(\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right)\right]
\end{aligned} \tag{14}$$

since the bits are all independent, the values of $\xi_i^\mu \xi_i^\nu$ (and $-\xi_i^\mu \xi_i^\nu$) get the values of $-1, 1$ with equal probability:

$$\mathbb{E}\left[\sum_{\nu\neq\mu} F\left(-\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right)\right] = \mathbb{E}\left[\sum_{\nu\neq\mu} F\left(\xi_i^\mu \xi_i^\nu + \sum_{j\neq i}^{N} \xi_j^\mu \xi_j^\nu\right)\right] \tag{15}$$

And:

$$\mathbb{E}\left[E(\xi^\mu) - E(\hat{\xi^\mu})\right] = (N-2)^n - N^n \tag{16}$$

(d) While the expected value of the sum in the final step of Eq. 13 is zero, it has some variance that scales with K (as this is the sum of $K-1$ independent random variables). This variance reflects the likelihood that a flipped bit will have lower energy that the original memory state, and thus that this bit reversal will not be corrected and that the pattern will not be stable.

Note: This question is technically more challenging but conceptually identical to the material provided in the mastery section.