Question 1 **1D model of gene auto-activation.** Consider a self-activated gene, *i.e.* a gene encoding for a protein which can bind to the promoter region of this same gene to enhance its transcription. The dynamics of this self-activated gene can be represented by the following ODE model of order 2:

$$\dot{m} = k_1 \frac{p}{K+p} - d_1 m \tag{1}$$

$$\dot{p} = k_2 m - d_2 p \tag{2}$$

where $m(t) \geq 0$ represents the mRNA concentration at time t, $p(t) \geq 0$ represents the protein concentration at time t, and the short-hand notation $\dot{x}$ stands for $\frac{dx}{dt}$. The parameters appearing in this model are defined as follows: $k_1 \geq 0$ represents maximal transcription rate, $K \geq 0$ the activation coefficient, $k_2 \geq 0$ the translation rate, $d_1 \geq 0$ the mRNA degradation rate, and $d_2 \geq 0$ the protein degradation rate.

It can be shown that the second order model (1)-(2) can be reduced to a **first order model** of the form:

$$\boxed{\dot{p} = \alpha \frac{p}{K+p} - d_2 p} \tag{3}$$

a) First order model (3) **and its fixed point(s) analysis** **/50**

i) Using the quasi-steady state approximation $\dot{m} = 0$, show how the model (1)-(2) can be reduced to the first order model (3) and give the analytical expression of $\alpha \geq 0$ in terms of the parameters in (1)-(2).

The quasi-steady-state approximation $\dot{m} = 0$ yields the algebraic relation $m = \frac{k_1}{d_1}\frac{p}{K+p}$, which, when injected into (2)*, yields* (3) *with $\alpha = \frac{k_1 k_2}{d_1}$.*

Marks: **20**

ii) Find the *analytical expression* of the fixed point(s) of (3). Based on this, determine how many fixed points the model described in (3) can have depending on the parameter $d_2 \geq 0$. (Remember that the concentration, p, is a non-negative quantity by definition).

Algebraically: *The fixed points of* (3) *are the roots of the scalar equation $\dot{p} = 0 = \alpha \frac{p}{K+p} - d_2 p$. Rearrangement of this expression yields $p(d_2(K+p) - \alpha) = 0$. Therefore the two fixed points are $\bar{p}_1 = 0$ and $\bar{p}_2 = \frac{\alpha}{d_2} - K$. Since p represents the concentration of a protein it must be a non-negative real number. Thus, $\bar{p}_2$ only makes physical sense as a second fixed point for $d_2 \leq \frac{\alpha}{K}$. Therefore, $\bar{p}_2$ only exists when $0 \leq d_2 \leq \frac{\alpha}{K}$.*

In summary:

- *For $0 \leq d_2 \leq \frac{\alpha}{K}$, there are two fixed points, $(\bar{p}_1, \bar{p}_2) = (0, \frac{\alpha}{d_2} - K)$.*
- *For $d_2 > \frac{\alpha}{K}$, there is only one fixed point, $\bar{p}_1 = 0$.*

Graphically:

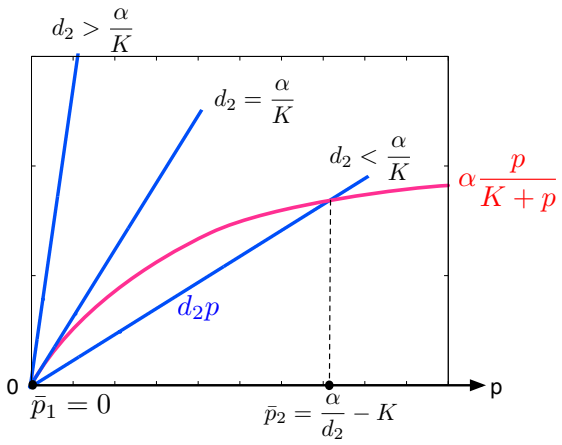

Fig. 1: Graphical analysis of the fixed points for an ODE model of order 1. The intersection(s) of the two curves $\alpha \frac{p}{K+p}$ and $d_2 p$ allow(s) to identify the location of the fixed points on the horizontal protein concentration (p) axis.

Marks:

30

b) Stability and bifurcation analysis of the first order model (3) **/50**

i) Using a graphical approach perform a stability analysis of (3). In particular, determine the direction of the flow on the p axis and, using this, determine the stability of each fixed point for the model given in (3).

Graphically: *The first order nonlinear differential equation in* (3) *allows us to easily evaluate the flow along the real line of protein concentrations p. For $\dot{p}$ to be positive we need to have $\alpha \frac{p}{K+p} - d_2 p > 0$ which is equivalent to $\alpha \frac{p}{K+p} > d_2 p$,* i.e. *$\dot{p}$ is positive where the curve $\alpha \frac{p}{K+p}$ lies above the curve $d_2 p$. Similarly, $\dot{p}$ is negative where the curve $\alpha \frac{p}{K+p}$ lies below the curve $d_2 p$. This allows us to draw the direction of the flow on the horizontal axis p (see Figure 2).*

Algebraically: *The local stability of the fixed points can be established by looking at the Jacobian evaluated at each fixed point, since, for a one-dimensional system, the Jacobian is scalar and represents the unique*

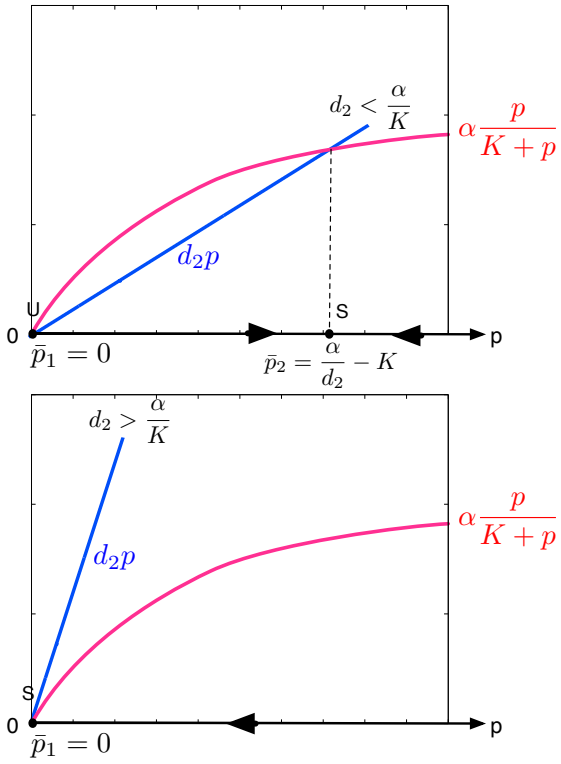

Fig. 2: Graphical stability analysis for an ODE model of order 1. The direction of the flow on the phase line is indicated on the horizontal protein concentration (p) axis. U denotes the unstable fixed point. S denotes the stable fixed point.

eigenvalue associated with the linearised system. The Jacobian is given by $J = \frac{\partial}{\partial p}\left(\alpha\frac{p}{K+p} - d_2 p\right) = \frac{\alpha(K+p)-\alpha p}{(K+p)^2} - d_2 = \frac{\alpha K}{(K+p)^2} - d_2$.

- *At the fixed point* $\bar{p}_1 = 0$, $J|_{p=\bar{p}_1=0} = \frac{\alpha}{K} - d_2$. *Therefore we have the following cases:*
  - $d_2 < \frac{\alpha}{K} \Rightarrow J > 0$ *and* $\bar{p}_1$ *is unstable.*
  - $d_2 = \frac{\alpha}{K} \Rightarrow J = 0$ *and the Hartman-Grobman theorem tells us we cannot conclude about the stability of the original nonlinear system using linearisation around the fixed point* $\bar{p}_1$.
  - $d_2 > \frac{\alpha}{K} \Rightarrow J < 0$ *and* $\bar{p}_1$ *is stable.*
- *At the fixed point* $\bar{p}_2 = \frac{\alpha}{d_2} - K$, $J|_{p=\bar{p}_2=\frac{\alpha}{d_2}-K} = d_2\left(\frac{K}{\alpha}d_2 - 1\right)$. *Note that* $\bar{p}_2$ *is only defined for* $0 < d_2 \leq \frac{\alpha}{K}$. *We thus have*
  - $0 < d_2 < \frac{\alpha}{K} \Rightarrow J < 0$ *and* $\bar{p}_2$ *is stable.*
  - $d_2 = \frac{\alpha}{K} \Rightarrow J = 0$ *and the Hartman-Grobman theorem tells us we cannot conclude about the stability of the original nonlinear system using linearisation around the fixed point* $\bar{p}_2$.
  - *(*$d_2 > \frac{\alpha}{K} \Rightarrow J > 0$ *and* $\bar{p}_2$ *is unstable. However we don't consider this case, since for* $d_2 > \frac{\alpha}{K}$, $\bar{p}_2$ *has negative values (and concentrations must be positive by definition).)*

From this algebraic analysis, we can see that the fixed points exchange stability at the critical bifurcation value $d_2 = \frac{\alpha}{K}$. *This is also coherent with the graphical analysis, which shows that a bifurcation occurs when the two curves* $\alpha\frac{p}{K+p}$ *and* $d_2 p$ *are tangent (the two fixed points exchange stability when they coincide at the critical bifurcation value), which occurs at* $d_2 = \frac{\alpha}{K}$.

(Note that imposing that the Jacobian is zero also corresponds in this case to imposing that the two curves touch tangentially (slopes of the curves are equal). This means that the two fixed point merge into one when $d_2 = \frac{\alpha}{K}$. *This is coherent with what we said before.)*

Marks:

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ii) Considering d_2 as the bifurcation parameter, draw a bifurcation diagram of (3). Clearly indicate on the bifurcation diagram the critical value of d_2 at which a bifurcation occurs.

Bifurcation diagram:

Remark (not asked in the question): *Strictly speaking this is a* transcritical bifurcation *as the two fixed points exchange stability at the critical value*

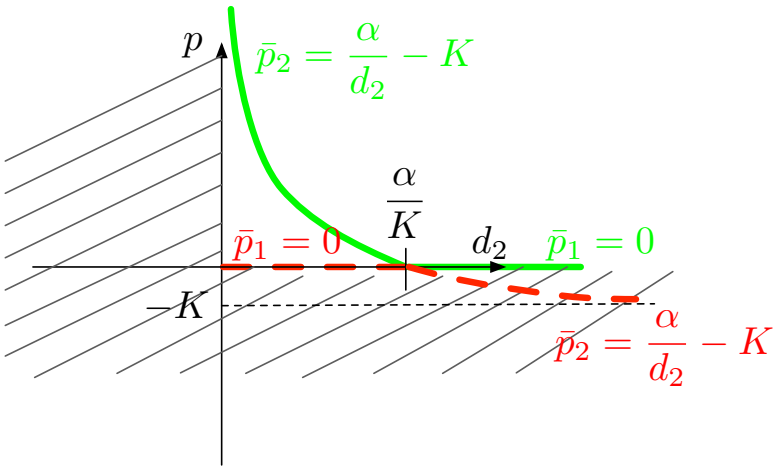

Fig. 3: Bifurcation diagram. Plain green lines denote loci of stable fixed points. Dashed red lines denote loci of unstable fixed points.

$d_2 = \frac{\alpha}{K}$. *However, beyond the critical value,* i.e. *for* $d_2 > \frac{\alpha}{K}$, *the fixed point* $\bar{p}_2$ *has negative values, which are not considered since* p *represents a concentration (which by definition is a positive quantity). Note that none of the two fixed points disappears at the bifurcation. Mathematically, they both exist for all values of* d_2. *The fact that* $\bar{p}_2$ *becomes negative, and thus non-physical, beyond the critical bifurcation value has no relevance for the type of bifurcation that occurs.*

Marks:

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Question 2 Short answer questions from both parts of the course

a) Consider a continuous-time, nonlinear Ordinary Differential Equation (ODE) model of the form $\dot{\boldsymbol{x}} = \boldsymbol{f}(\boldsymbol{x})$. Give the different attractors that this ODE model can have when: **/15**

i) $\boldsymbol{x} \in \mathbb{R}$, *i.e.* the ODE model is 1D

ii) $\boldsymbol{x} \in \mathbb{R}^2$, *i.e.* the ODE model is 2D

iii) $\boldsymbol{x} \in \mathbb{R}^n$, with $n \geq 3$, *i.e.* the ODE model is 3D or higher

Solution:

i) *Systems of order 1 can only converge to fixed points or to infinity.*

ii) *Systems of order 2 can additionally converge to limit cycle attractors.*

iii) *Systems of order 3 or higher can additionally converge to quasi-periodic or chaotic attractors.*

Marks:

15

b) Consider the second order linear dynamical system:

$$\dot{\boldsymbol{x}} = A\boldsymbol{x}, \quad \text{with} \quad A = \begin{pmatrix} -k & k \\ -k & 1 \end{pmatrix}, \quad \text{and} \quad \boldsymbol{x} \in \mathbb{R}^2,$$

where $k \in \mathbb{R}$ is an unknown, real (not complex or imaginary) parameter.

Show that for $-\frac{1}{3} \leq k \leq 1$, trajectories of the phase plane will approach or escape the origin exponentially, without any spiralling (*i.e.* without any rotation). *Hint: This is linked to a property of the eigenvalues of* A. **/35**

Solution:

The linear system $\dot{x} = Ax$ *as a single fixed point at (0,0), for* $k \neq 0, k \neq 1$.

Trajectories spiral if eigenvalues are complex. The eigenvalues $\lambda_{1,2}$ *of A are given by the roots of the characteristic equation*

$$0 = \textit{det}(\lambda I - A) = \textit{det}\begin{pmatrix} \lambda + k & -k \\ k & \lambda - 1 \end{pmatrix} = (\lambda+k)(\lambda-1)+k^2 = \lambda^2-(1-k)\lambda+k^2-k.$$

This yields, $\lambda_{1,2} = \frac{1-k}{2} \pm \frac{1}{2}\sqrt{(1-k)(1+3k)}$.

Therefore $\lambda_{1,2} \in \mathbb{R}$ *if* $(1-k)(1+3k) \geq 0$, *which is true for* $-\frac{1}{3} \leq k \leq 1$.

Marks:

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c) **i)** Draw a social network where everybody has exactly a node degree of 3 and the *global* clustering coefficient is exactly $\frac{1}{4}$. **/25**

See scanned sheet below.

Marks:

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ii) Explain the difference between null-recurrent and positive recurrent Markov process states. Illustrate your explanation with a suitable example. **/25**

If a state is recurrent, we say that the state is positive recurrent if the expected amount of time between recurrences (when the chain is in that state) is finite. A state that is recurrent but not positive recurrent is called null recurrent. An example of a null recurrent state appears in the simple random walk. The initial starting state is recurrent, but it turns out that the (this and all other) states are in fact null recurrent.

Marks:

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Question 3 **Fungi** are complex eukaryotic organisms that can undergo reproduction in more than one way. The life-cycle of fungi can be represented as a Markov Process with state transitions occurring about every week. The following 6 states are known: (G) Germination, (R) Rest, (H) Heterokaryotic, (M) Meiosis, (S) Sporing, (D) Death. All fungi are "born" in the Germination state. Here we model a species of fungi that has two reproductive strategies: **1.** Sporing, that is asexual reproduction through spores (S); and **2.** Sexual reproduction through mating (H, M). The transition probabilities to other states are given as follows:

$$p_{GR} = \frac{1}{2} \quad p_{RH} = \tfrac{1}{4} \quad p_{RD} = \frac{1}{8}$$
$$p_{RS} = \frac{1}{4} \quad p_{SR} = \tfrac{1}{2} \quad p_{SG} = \frac{1}{2}$$
$$p_{HM} = \frac{1}{2} \quad p_{MR} = \tfrac{1}{2} \quad p_{MG} = \frac{1}{2}$$

All calculations should be doable using fractions.

a) Sketch out the Markov process including all states and all possible transitions. Label the states and transitions. Mark the absorbing states. Then, write out the transition probability matrix using the Markov matrix notation used in the course. **/30**

See scanned sheet below.

Marks:

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b) Derive the mean life time in weeks of this species of fungi based on the Markov Process model. Use first-step analysis on the Markov chain to derive this result and explain your derivation. **/35**

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c) Derive the mean number of weeks these fungi are in a reproductive state. Use first-step analysis on the Markov chain to derive this result and explain your derivation. **/35**

See scanned sheet below.

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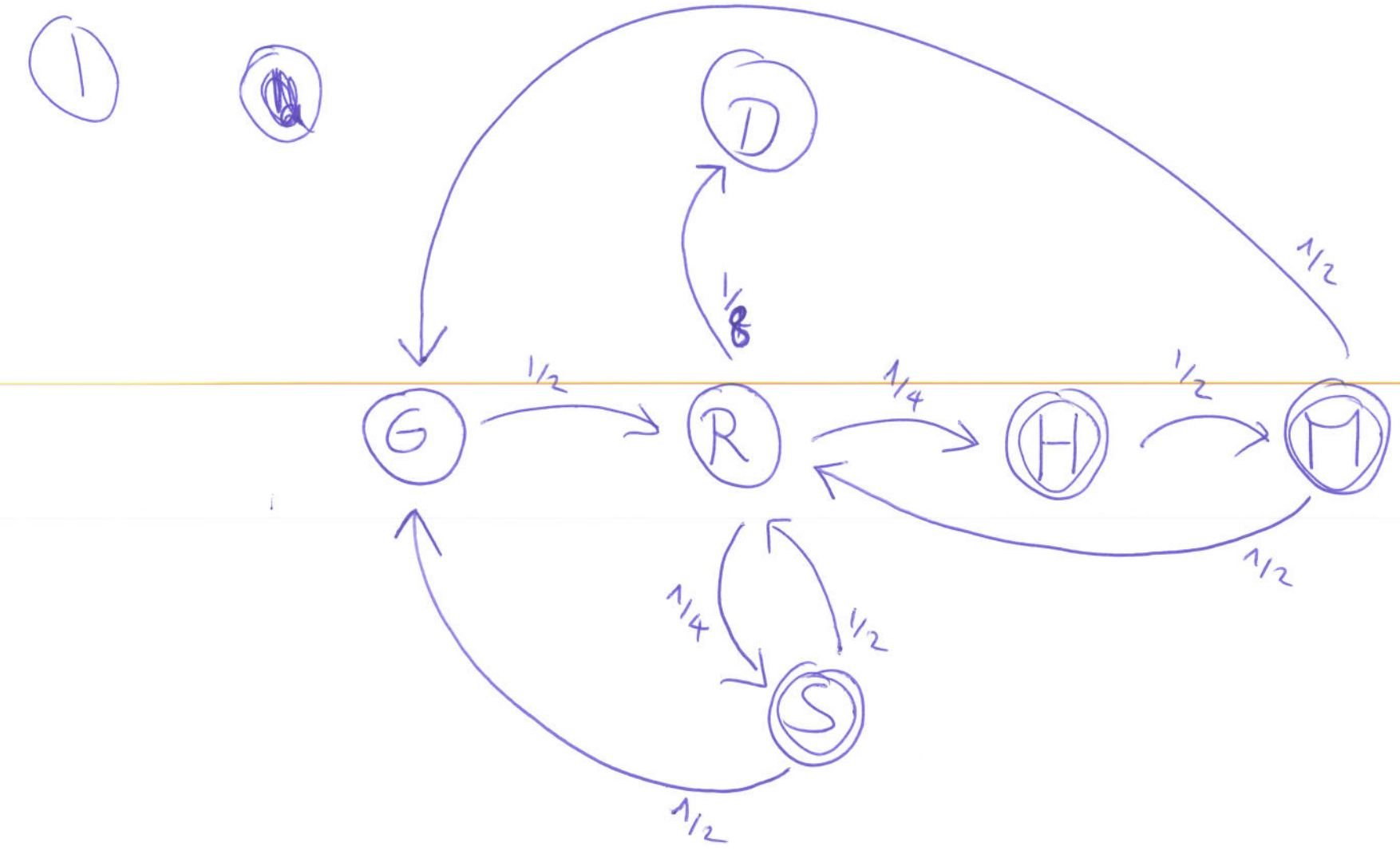


b.)

	G	R	H	M	S	D
G	1/2	0	0	1/2	1/2	0
R	1/2	3/8	0	1/2	1/2	0
H	0	1/4	1/2	0	0	0
M	0	0	1/2	0	0	0
S	0	1/4	0	0	0	1
D	0	1/8	0	0	0	0

d.) Ansatz: n_i number of visits to reproductive state, (S, H, M)

so $n_R = \frac{1}{4} \cdot n_H + \frac{1}{4} \cdot n_S + \frac{1}{8} \cdot 0$

$n_H = \frac{1}{2} \cdot n_M + 1 + \frac{1}{2} \cdot n_H$

$n_M = \frac{1}{2} \cdot n_G + \frac{1}{2} \cdot n_R + 1$

$n_S = \frac{1}{2} \cdot n_R + \frac{1}{2} \cdot n_G + 1$

$n_G = \frac{1}{2} \cdot n_R + \frac{1}{2} \cdot n_G$

Solve for n_G.

$n_G \approx 8 \quad (7.84)$

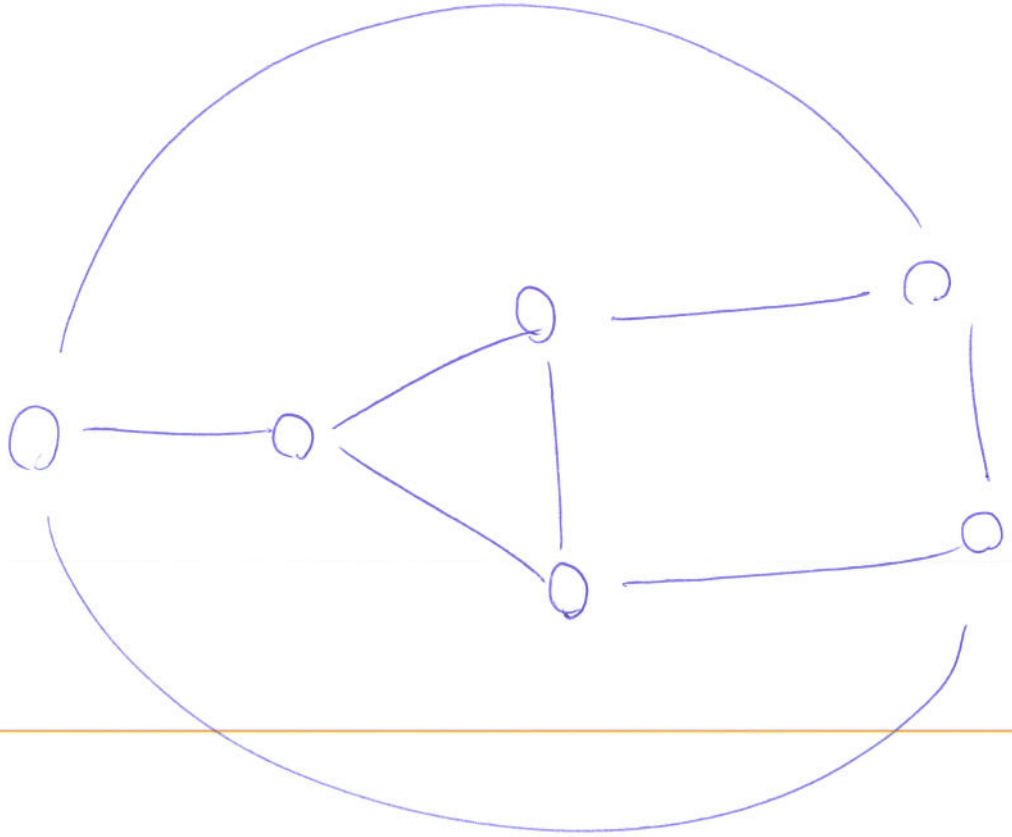
c.) Ansatz: τ_i time to absorption ~~starting~~ from state i

~~$\tau_D = p_{RD} \cdot \tau_R + 1$~~

1. $\tau_R = \tau_H \cdot p_{RH} + \tau_S \cdot p_{RS} + p_{RD} \cdot \underline{1} + \underline{1}$
   $+ \tau_R \cdot p_{RR}$
2. $\tau_H = \tau_M \cdot p_{HM} + \underline{1} + \tau_H \cdot p_{HH}$
3. $\tau_M = p_{M6} \cdot \tau_6 + p_{MR} \cdot \tau_R + 1$
4. $\tau_S = p_{SR} \cdot \tau_R + p_{S6} \cdot \tau_6 + \underline{1}$
5. $\tau_6 = \tau_R \cdot p_{6R} + \underline{1} + \tau_6 \cdot p_{66}$

Solve for τ_6.

$\tau_6 \approx$ ~~20~~ 21 (20.59)



(9 2)

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