UNIVERSITY OF OSLO

Faculty of Mathematics and Natural Sciences

Examination in: MAT-BIO2100 — Matematisk Biologi

Day of examination: Wednesday 6 June 2012

Examination hours: 09.00 – 13.00.

This problem set consists of 6 pages.

Appendices: None

Permitted aids: None

Please make sure that your copy of the problem set is complete before you attempt to answer anything.

Problem 1

The bacterium *B. Subtilis* has two distinct states– a normal reproductive state (expressed under normal levels of nutrients) and a spore (expressed under starvation conditions). Very different sets of genes are expressed for different states. The transition of the bacterium from a normal state to a spore state involves a network shown in figure 1. Here, X_1 is the master regulator (transcription factor), that together with Y_1 controls two sets of genes Z_1 and X_2. In turn, X_2 together with Y_2 regulates the expression of Z_2. Note that the target genes of the system are Z_1 and Z_2. The logic used in both the feed forward loops is **AND**.

(i.) **Wild type:** Write down a model describing the dynamics of Y_1, Z_1, X_2, Y_2 and Z_2 in time. Assume that the maximum levels of expression and decay rates of Y_1, X_2, Y_2 and Z_2 are $\beta_{Y_1}, \beta_{X_2}, \beta_{Y_2}, \beta_{Z_2}$ and $\alpha_{Y_1}, \alpha_{X_2}, \alpha_{Y_2}, \alpha_{Z_2}$, respectively. Z_2 is maximally expressed at two different levels: one when it is activated by X_1 and not repressed by Y_1, given by β_{Z_1} and another level of expression when it is activated by X_1 and repressed by Y_1, given by $\overline{\beta}_{Z_1}$ with $\overline{\beta}_{Z_1} < \beta_{Z_1}$. The decay rate for Z_1 is α_{Z_1}. Use logic functions for activation and repression with activation thresholds $K_{X_1Y_1}$ for Y_1, $K_{X_1Z_1}$ for Z_1, $K_{X_1X_2}, K_{Y_1X_2}$ for X_2, $K_{X_2Y_2}$ for Y_2 and $K_{X_2Z_2}, K_{Y_2Z_2}$ for Z_2. Similarly, use repression threshold $K_{Y_1Z_1}$ for Z_1.

(ii.) (**Control:**): As a control, consider a network (shown in figure 2) formed by knocking the gene Y_1. Write down a model describing the dynamics of Z_1, X_2, Y_2, Z_2. Use the same maximum levels of expression, decay rates and thresholds as the previous question for all proteins except for

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Z_1. For Z_1, use a maximum level of expression of $\overline{\beta}_{Z_1}$ and a decay rate of α_{Z_1}.

(iii.) **Experiment 1:** Consider an experimental situation where the initial values for Y_1, Z_1, X_2, Y_2 and Z_2 is zero. Assume that there is full signal

$$X_1(t) \equiv S, \quad \forall t > 0.$$

Assuming that $S > K_{X_1Y_1}, K_{X_1Z_1}, K_{X_1X_2}$, write down the time dynamics of Z_1, Z_2 for both the wild type as well as the control. Calculate the response time of Z_1 for both the wild type as well as the control.

(iv.) **Experiment 2:** Consider an experimental situation where the initial values for Y_1, Z_1, X_2, Y_2 and Z_2 is zero. Assume that the signal for X_1 is of the form:

$$X_1(t) = \begin{cases} S, & \text{if } 0 < t \leq \frac{t^*}{2}, \\ 0, & \text{otherwise} \end{cases} \tag{1}$$

Here, t^* is given by

$$t^* = \frac{1}{\alpha_{Y_1}} \log\left(\frac{Y_1^{st}}{Y_1^{st} - K_{Y_1X_2}}\right), \quad Y_1^{st} = \frac{\beta_{Y_1}}{\alpha_{Y_1}}.$$

Write down the dynamics of Z_1, Z_2 as functions of time for both the wild type as well as the control in this case.

(v.) Using the above two experiments, describe possible functional advantages that the wild type network (shown in figure 1) will confer to the bacterium compared to the control network (shown in 2).

Problem 2

The nose-touch system in the worm *C. Elegans* is depicted in figure 3. Here, the nose and the touch for noxious chemicals is processed by the neurons **FLP** and **ASH**. The inputs are send to the regulating neuron **AVD** as well as the motor neuron **AVA**. The motor neuron **AVA** modulates movement in the worm in response the detection of noxious chemicals. Given the multiple inputs for the downstream neurons, one can approximate the activation of **AVD** using an **OR** logic for its two input signals **FLP** and **ASH**. Similarly the activation of the motor neuron **AVA** is based on
(FLP OR ASH) AND AVD.

(i.) **Wild type:** Write down a model describing the dynamics of the transmembrane voltage potentials for **AVD** and **AVA**. Here, assume that β_Y, β_Z are the maximum levels of activity for **AVD** and

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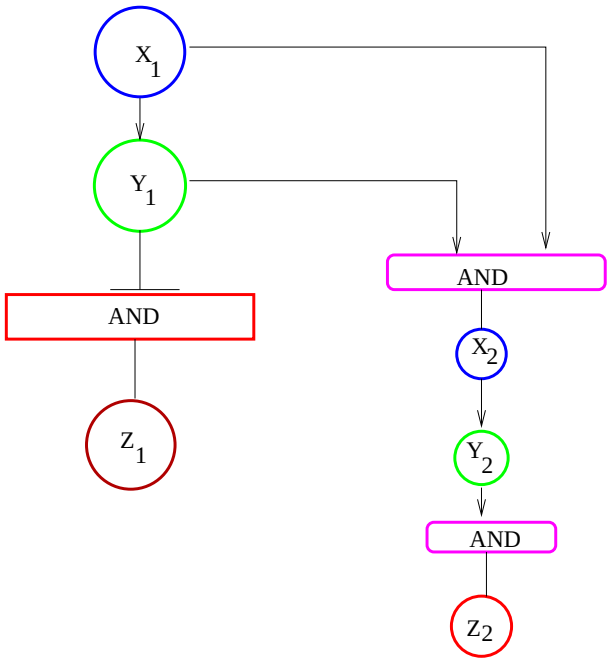

Figure 1: Wildtype sporulation network for B. Subtilies

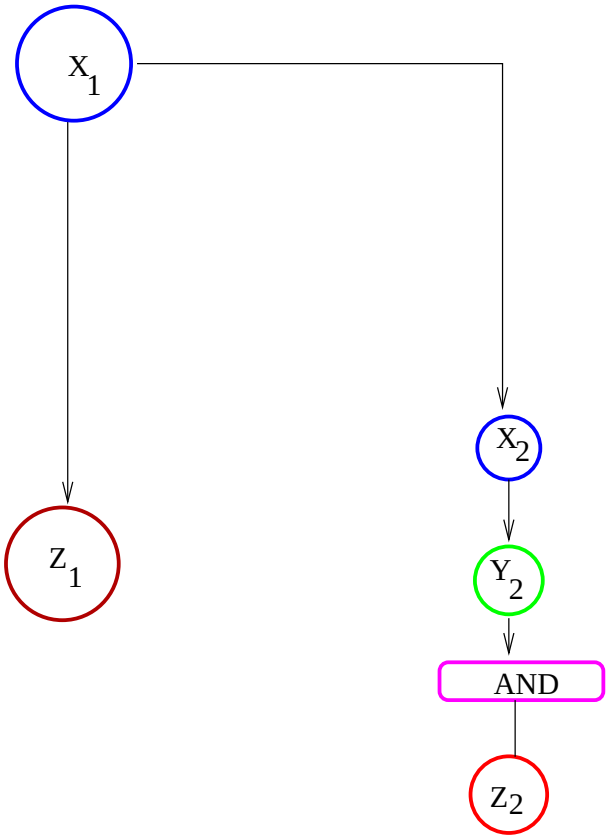

Figure 2: Control sporulation network for B. Subtilies

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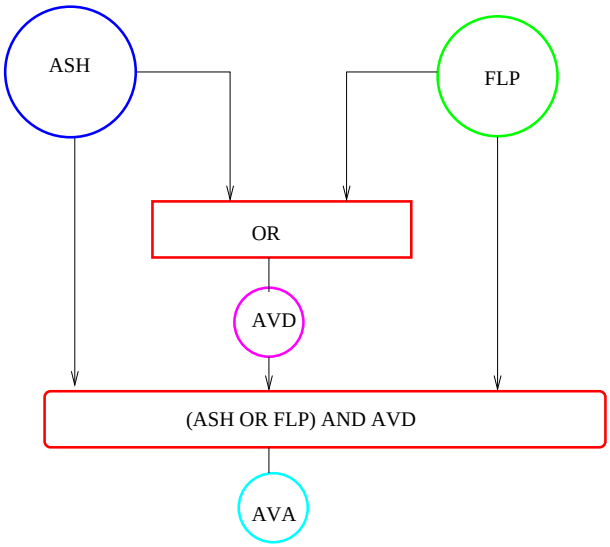

Figure 3: Wildtype nose-touch network for C. Elegans

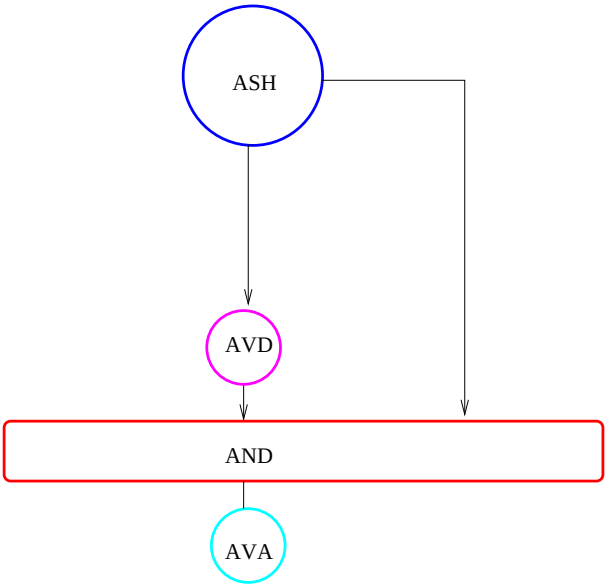

Figure 4: Control nose-touch network for C. Elegans

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AVA, respectively. Similarly, α_Y, α_Z are the leakage currents for **AVD** and **AVA**, respectively. Use thresholds K_{X_1Y}, K_{X_2Y} for the activation of **AVD** by **ASH** and **FLP**, respectively. Use thresholds $K_{X_1Z}, K_{X_2Z}, K_{YZ}$ for the activation of **AVA** by **ASH**, **FLP** and **AVD**, respectively.

(ii.) **Control:** As a control, we knock out one of the inputs **FLP** and retain the network shown in figure 4. Now, the logic for the activation of **AVA** is **ASH AND AVD**. Write down a model describing the dynamics of the transmembrane voltage potentials for **AVD** and **AVA**. The maximum level of neuronal activity and the leakage current for both these neurons is assumed to be same as the previous question as are the different thresholds of activation.

(iii.) **Experiment** 1**:** Consider the following input signals:

$$X_1(t) = \begin{cases} S, & \text{if } 1 < t \leq 1 + \frac{3t^*}{4}, \\ 0, & \text{otherwise,} \end{cases} \tag{2}$$

and

$$X_2(t) = \begin{cases} \bar{S}, & \text{if } 2 + \frac{t^*}{2} < t \leq 2 + \frac{5t^*}{4}, \\ 0, & \text{otherwise,} \end{cases} \tag{3}$$

with

$$t^* = \frac{1}{\alpha_Y} \log\left(\frac{Y^{st}}{Y^{st} - K_{YZ}}\right), \quad Y^{st} = \frac{\beta_Y}{\alpha_Y}.$$

Here X_1, X_2 denotes the transmembrane voltage potential for **ASH** and **FLP**, respectively. Write down the dynamics of the transmembrane potentials of **AVD** and **AVA** as functions of time, for both the wild type as well as the control.

(iv.) **Experiment** 2**:** Consider the following input signals:

$$X_1(t) = \begin{cases} S, & \text{if } 1 < t \leq 1 + \frac{3t^*}{4}, \\ 0, & \text{otherwise,} \end{cases} \tag{4}$$

and

$$X_2(t) = \begin{cases} \bar{S}, & \text{if } 1 + \frac{t^*}{2} < t \leq 1 + \frac{5t^*}{4}, \\ 0, & \text{otherwise,} \end{cases} \tag{5}$$

with

$$t^* = \frac{1}{\alpha_Y} \log\left(\frac{Y^{st}}{Y^{st} - K_{YZ}}\right), \quad Y^{st} = \frac{\beta_Y}{\alpha_Y}.$$

Here X_1, X_2 denotes the transmembrane voltage potential for **ASH** and **FLP**, respectively. Write down the dynamics of the transmembrane potentials of **AVD** and **AVA** as functions of time, for both the wild type as well as the control.

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(v.) Based on the above two experiments, describe what functional advantages are conferred to *C. Elegans* by the wild type neuronal network (shown in figure 3) as opposed to the control neuronal network (shown in figure 4).

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