580.439/639 Midterm Solutions, 2011

Problem 1

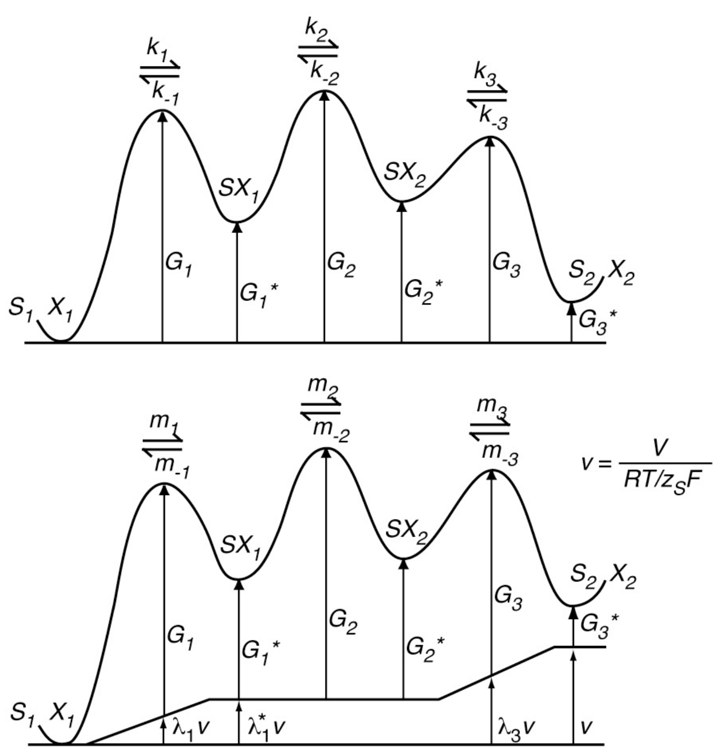
Part a) The flux equations assuming that all fluxes are equal. Note that the unknowns in this system are J, X_1, SX_1, SX_2, and X_2, so five equations are needed.

$$
\begin{aligned}
J &= k_1 S_1 X_1 - k_{-1}\, SX_1 \\
J &= k_2\, SX_1 - k_{-2}\, SX_2 \\
J &= k_3\, SX_2 - k_{-3}\, S_2\, X_2 \\
J &= -k_{-4}\, X_1 + k_4\, X_2 \\
T &= X_1 + SX_1 + SX_2 + X_2
\end{aligned}
$$

Note the sign of the terms in the fourth equation. These are dictated by the necessity that the fluxes be continuous in one loop direction.

Part b) The solution to the equations above will take the form of equation (2) in the problem set. The numerator of that equation satisfies the first condition, that the flux go to zero when S is at equilibrium (which means $S_1 = S_2$ for an uncharged substrate). The fact that the ratio of rate constants in this equation equals 1 from microscopic reversibility makes the equilibrium condition hold. The denominator contains terms in S_1 and S_2 which are needed to satisfy the condition that the flux saturate, made necessary by the fixed total amount of transporter T.

Part c) The rate constants depend on membrane potential only if charge is moved through a change in potential. The problem statement specifically said that the substrate does not move when the transporter changes conformation (from SX_1 to SX_2), so the only voltage-dependent rate constants are k_1, k_{-1}, k_3, and k_{-3}.



The barrier systems at right are sufficient to model this situation. The barriers are shown without membrane potential (or for an uncharged substrate) in the top plot and with membrane potential below. Note that the membrane potential is kept constant through states SX_1 and SX_2 to represent the fact that no charge moves during these reactions.

The rate constants from this barrier diagram are listed below. Rate constants k_i are for no membrane potential (top barrier model) and rate constants m_i include the effect of membrane potential (bottom barriers).

$$
\begin{array}{llll}
k_1 = \alpha e^{-G_1/RT} & m_1 = k_1 e^{-\lambda_1 v} & k_{-1} = \alpha e^{-(G_1 - G_1*)/RT} & m_{-1} = k_{-1} e^{-(\lambda_1 - \lambda_1*)v} \\
k_2 = \alpha e^{-(G_2 - G_1*)/RT} & m_2 = k_2 & k_{-2} = \alpha e^{-(G_2 - G_2*)/RT} & m_{-2} = k_{-2} \\
k_3 = \alpha e^{-(G_3 - G_2*)/RT} & m_3 = k_3 e^{-(\lambda_3 - \lambda_1*)v} & k_{-3} = \alpha e^{-(G_3 - G_3*)/RT} & m_{-3} = k_{-3} e^{-(\lambda_3 - 1)v}
\end{array}
$$

The ratio of rate constants for the m_i constants is

$$
\frac{m_{-1}\, m_{-2}\, m_{-3}\, m_{-4}}{m_1\, m_2\, m_3\, m_4} = \frac{k_{-1} e^{-(\lambda_1 - \lambda_1*)v}\, k_{-2}\, k_{-3} e^{-(\lambda_3 - 1)v}\, k_{-4}}{k_1 e^{-\lambda_1 v}\, k_2\, k_3 e^{-(\lambda_3 - \lambda_1*)v}\, k_{-4}} = e^{v}
$$

where the final step follows from the fact that the ratio of the k rate constants is 1 in the absence of membrane-potential effects

The numerator of the flux equation (2) is now $S_1 - S_2 e^{v}$. S is at equilibrium when $v = \dfrac{V}{RT/z_S F} = \ln \dfrac{S_1}{S_2}$, at which point the numerator of the flux equation is zero, consistent with equilibrium thermodynamics.

Part d) If the un-bound transporter cannot change confirmation flux must go to zero. In that case, the only way a transporter can transition between X_1 and X_2 is if a substrate molecule moves through the membrane. Thus the number of molecules moving from S_1 to S_2 must be equal, giving zero net flux. Note that a substantial interchange of substrate molecules could occur in this case.

Problem 2

Part a) The nullclines are

$$
y_{x\,nullcline} = x^2 - 2
$$

$$
y_{y\,nullcline} = x
$$

and are plotted in the phase plane on the next page (blue and green lines). The equilibrium points, where $y_{x\,nullcline} = y_{y\,nullcline}$, are the solutions of

$$
x^2 - x - 2 = 0
$$

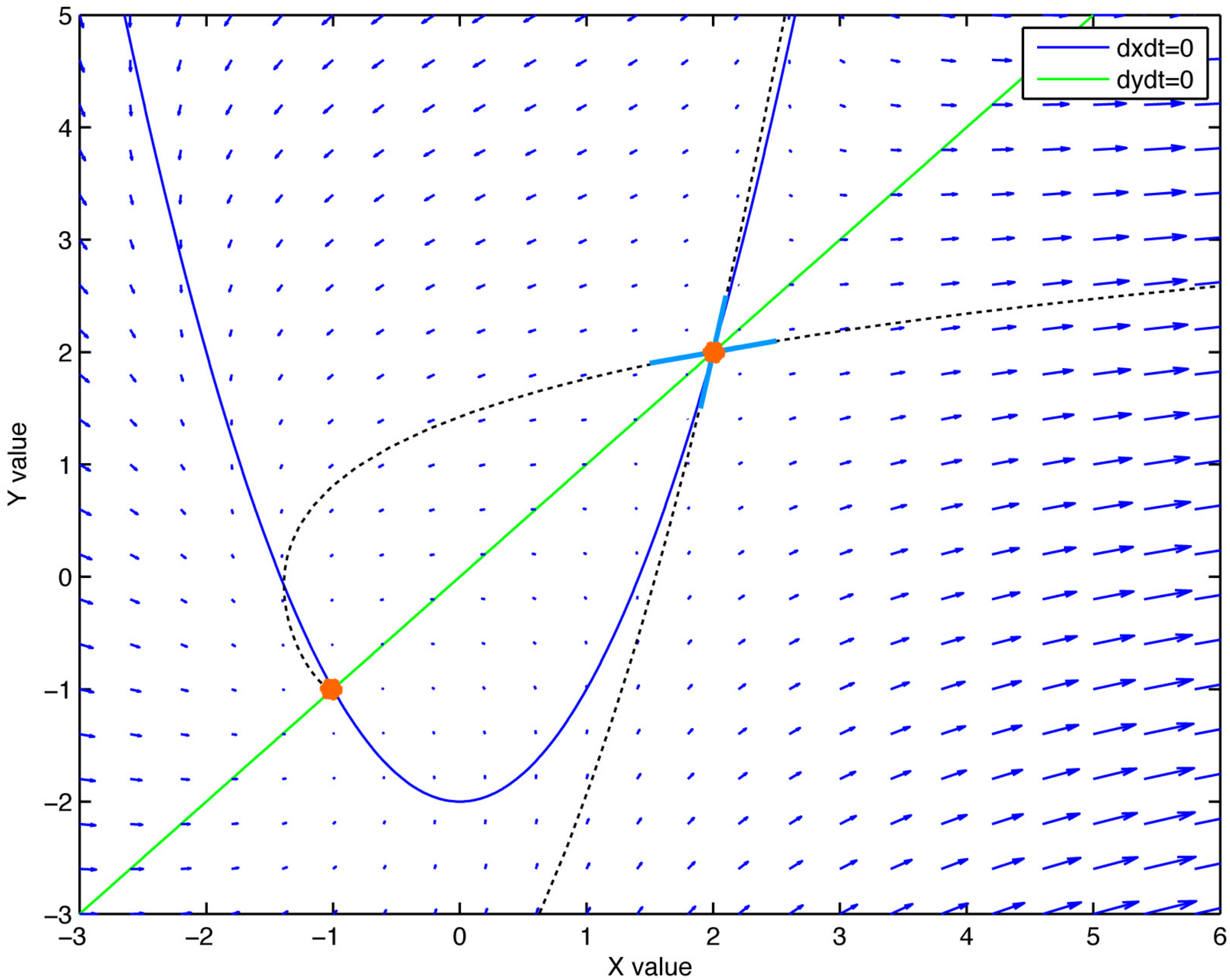
which are x = 2, y=2 and x = -1, y = -1 for the two equilibrium points, orange dots in the phase plane. The phase plane also shows trajectory directions in detail. Of course, these are not expected as part of the test answer, although vectors showing the general directions of trajectories in the various regions defined by the nullclines should have been included.

Part b) The Jacobians at the two equilibrium points are

$$
J = \begin{bmatrix} 2x & -1 \\ 1 & -1 \end{bmatrix} \qquad J_1 = \begin{bmatrix} 4 & -1 \\ 1 & -1 \end{bmatrix} \qquad J_2 = \begin{bmatrix} -2 & -1 \\ 1 & -1 \end{bmatrix}
$$

Computing the eigenvalues as the roots of det(J-λI) = 0 gives

EP_1: $\lambda=(3 \pm 21^{0.5})/2$, a saddle node and EP_2: $\lambda = (-3 \pm j\, 3^{0.5})/2$, a stable spiral



To compute the eigenvectors, solve the usual equations, as below for the saddle node.

$$\begin{bmatrix} 4 & -1 \\ 1 & -1 \end{bmatrix} \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} = \begin{bmatrix} \lambda e_1 \\ \lambda e_2 \end{bmatrix} \Rightarrow e_1 = e_2 (5 \pm 21^{0.5}) / 2 = 4.8 e_2 \text{ (unstable) and } = 0.2 e_2 \text{ (stable)}$$

As usual, the eigenvectors are specified only as to direction, not amplitude. The eigenvectors point in the directions of the unstable and stable manifolds at a saddle. They are shown on the phase plane above as heavy light blue lines, from which it is apparent that the eigenvector directions correspond to the dashed trajectories provided in the exam paper. Given that trajectories are unique in the phase plane, this result makes it reasonable to assume that the dashed trajectories are the stable and unstable manifolds of the saddle (in fact they are those manifolds).

One unstable manifold ends at the stable equilibrium point, the other goes off to infinity. The stable manifolds divide the phase plane as shown into a region containing the stable equilibrium point and an unstable region.

Part c) From index theory, a limit cycle would have to encircle the stable equilibrium point and not the saddle. However the unstable manifold discussed above prevents that from occurring, since trajectories cannot cross in the phase plane. This same conclusion can also be drawn from a careful inspection of the trajectory directions (blue arrows), although one cannot be sure of such an argument.

Part d) The stable manifolds of the saddle separate the phase plane into two regions. All trajectories in the left hand one, which contains the stable equilibrium point, must end in the stable equilibrium because (1) trajectory directions are toward the equilibrium point (and not out of the phase plane) and (2) there is no limit cycle. With a computer, a few trial trajectories can be computed; these are shown on the phase plane below in red, supporting this conclusion.