**Problem Set #3**
MB&B361/562
Spring 2024
**DUE: March 8, 2024**

You may consult with your classmates and the TAs, but all scripts and answers must be your own. We will look at the scripts and answers closely 🕵️. **Be sure you answer all parts of the questions (even the subparts can ask multiple questions)**.

This question is based on the Hudspeth (2014) and Reichenbach & Hudspeth (2014) papers. You don't need to read either, but for details of the model look at the hair cell lecture keynote presentation and hair cell notes on Canvas. This is the full model and not the simplified model that I went over in class. The full model includes the geometry of the bundle, specifically:
- there is geometric conversion factor ($\gamma$) between bundle movement and shear between the sterocilia (which stresses the gating spring that open the channel).
- there are $N$ stereocilia and channels
- the bases of the stereocilia have a stiffness ($\kappa_S$) that tends to restore the bundle to the upright position
- the adaptation motors have a maximum speed (this gets normalized away anyway)


Hudspeth, A.J. (2014). Integrating the active process of hair cells with cochlear function. *Nat Rev Neurosci 15*, 600–614.
Reichenbach, T., and Hudspeth, A.J. (2014). The physics of hearing: fluid mechanics and the active process of the inner ear. Rep Prog Phys *77*, 076601.


You are going to show that calcium feedback is necessary for hair-bundle oscillation in the Hudspeth model. In the simplified model that I went over (Slide 18 in the presentation), it was assumed that the force of the adaptation motor depends on the probability of the channel being open. The way that works in reality is that when the channel opens, calcium comes in and inhibits the motor. In this way the channel's opening feed backs on the adaptation.

The normalized dynamical equations (from the Lecture 11 KeyNote – more details in the Lecture 11 notes) are

$$\bar{X}' = \bar{F} - \bar{\kappa}_s(\bar{X} - \bar{X}_s) - N\gamma[\bar{y} - p] = g(\bar{X}, \bar{y})$$

$$\bar{y}' = \bar{f}_1\bar{\xi} + \gamma[\bar{F} - \bar{\kappa}_s(\bar{X} - \bar{X}_s)] - \bar{y}\left[N\gamma^2 + \bar{\xi}\right] + p\left[N\gamma^2 + \bar{\xi}\left(1 - C\bar{f}_1\right)\right] = h(\bar{X}, \bar{y})$$

where $\bar{X}$ is the position of the bundle and $\bar{y}$ is the strain in the gating spring. The prime ($'$) denotes the time derivative.

We also have an expression for the channel open probability ($p$):

$$p = \frac{1}{1 + A\exp\left[-\alpha\bar{y}\right]} \qquad \alpha = \frac{\kappa d^2}{kT}, \quad \frac{dp}{d\bar{y}} = \alpha p(1 - p)$$

$\alpha$ determines how sensitively the open probability depends on position, $X$. If $\alpha$ is large enough the stiffness can be negative (and oscillations possible).

$C$ is the feedback from calcium entering the channel and weakening the adaptation motor. It is also a key parameter which has to be large enough for oscillations to occur.

If $\bar{y}_0$ is the strain in the gating spring when the tension in the gating spring equals the motor force and $p_0$ is the channel open probability at this strain, then

$$A = \frac{1-p_0}{p_0}\exp\left[+\alpha\bar{y}_0\right]$$

$$\bar{y}_0 = \bar{f}_1(1 - Cp_0) + p_0 \qquad \text{note that } \bar{y}_0 \text{ depends on } C$$

$$\bar{X}_S = \frac{N\gamma}{\bar{\kappa}_S}(\bar{y}_0 - p_0)$$

The following **unchanging** parameters are used

| | |
|---|---|
| $\bar{F} = 0$ | external force |
| $\gamma = 1/\sqrt{50}$ | geometric factor |
| $N = 50$ | number of channels and stereocilia |
| $\bar{\kappa}_s = 1$ | stiffness of the stereociliary pivot springs |
| $\bar{\xi} = 1$ | damping from the fluid |
| $\bar{f}_1 = 1$ | maximum motor force |
| $p_0 = 0.5$ | open probability at rest in the absence of external force |

The goal of this Problem Set is to determine how stability depends on the following two **free** parameters:

| | |
|---|---|
| $C$ | sensitivity of motor force on calcium (feedback) |
| $\alpha$ | sensitivity of open probability on gating spring tension |

The idea with calcium is that when the channel opens, calcium enters the cell and binds to the adaptation motor, reducing its force. This feedback is necessary for hair cell oscillations, as we will see.

First note that $\bar{X} = 0$ and $\bar{y} = \bar{y}_0 = (1 - Cp_0) + p_0$ is a fixed point. There is a lot of algebra, but you don't need to do it!

(a) (2 points) Calculate the trace and determinant of the Jacobian matrix at the fixed point, using the values of the unchanging parameters. Remember that the Jacobian is the linearization of the non-linear equations:

$$\begin{pmatrix} \frac{\partial g}{\partial \bar{X}} & \frac{\partial g}{\partial \bar{y}} \\ \frac{\partial h}{\partial \bar{X}} & \frac{\partial h}{\partial \bar{y}} \end{pmatrix}$$

Express the trace and determinant in terms of $\alpha$ and $C$ ($\bar{y}_0$ should not appear in these expressions; substitute $\bar{y}_0 = (1 - 0.5C) + 0.5$).

(b) (2 points). For $C = 0$, there are critical values of $\alpha$ where the trace and determinant of the Jacobian change sign (and the system switches between stability states). For example,

| $C = 0$ | tr | det | stable at fixed point? |
|---|---|---|---|
| $\alpha < 4$ | <0 | >0 | yes |
| $4 < \alpha < 6$ | <0 | <0 | no |
| $\alpha > 6$ | >0 | <0 | no |

Make a similar table for $C = 0.8$. (i.e. find the critical values of $\alpha$ where the tr and det change signs.

(c) (3 points) Write a MatLab livescript (i.e., .mlx) that solves the dynamical equations for the following values of $C$ and $\alpha$.
(i) $C = 0$ and $\alpha = 2, 5, 8$
(ii) $C = 0.8$ and $\alpha = 8, 15, 25$
(iii) $C = 1$ and $\alpha = 10, 15, 25$

Here is some barebones code (which works), though you have to write the plotting routines. It uses ode15s, solves up to 100 s and has initial conditions near the fixed point ($\bar{X}_0 = 2$ and $\bar{y}_0 = 1.1$).

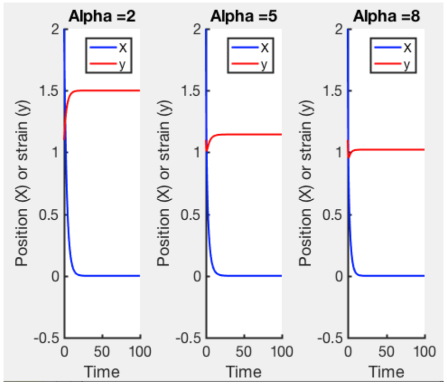
```
%%Parameters
F = 0;
G = 1/(50^(1/2));
N = 50;
Ks = 1;
neta = 1;
f1 = 1;
p0 = .5;

%% Solutions
% Case 1: C=0; al = [2 5 8]
% Case 2: C = 0.8; al = [8 15 25];

% Formulas for other constants
    y0 = f1*(1-C*p0) + p0;
    Xs = ((N * G)/Ks) * (y0-p0);
    A = (1-p0)/p0*exp(al*y0);

    %Equation
    dy=@(t,y)[F-Ks*(y(1)-Xs)-(N*G)*(y(2)-(1/(1+A*exp(-al*y(2)))));...
        (f1*neta) + G*(F-Ks*(y(1)-Xs)) - y(2)*(N*G^2 + neta) + ...
        (1/(1+A*exp(-al*y(2))))*(N*G^2 + neta*(1-C*f1))];
    [T,Y] = ode15s(dy,[0 100],[2 1.1]);
```

Plot $\bar{X}(t)$ and $\bar{y}(t)$ on the same plot with time on the *x*-axis.
For $C = 0$ It should look like this:




If you like, use `subplot(1,3,ii)` with ii =1, 2, 3

Save your mlx as a .pdf and hand in.

(d) (2 points). Add a 5th column to the tables for $C = 0$ and $C = 0.8$.
For $C = 0$ it looks like:

| $C = 0$ | tr | det | stable at fixed point? | oscillatory? |
|---|---|---|---|---|
| $\alpha = 2$ | <0 | >0 | yes | no |
| $\alpha = 5$ | <0 | <0 | no | no |
| $\alpha = 8$ | >0 | <0 | no | no |

The lower two rows are unstable, what happens to the solution (look at final value of $\bar{y}$).

Make a similar table for $C = 0.8$. with rows for $\alpha = 8, 15, 25$

Explain in words why $C$ and $\alpha$ must exceed minimum values to obtain instability and oscillations. If necessary try other values of $C$ and $\alpha$ e.g. $C = 0.5$, $\alpha = 6, 10, 12$ and $C = 1$, $\alpha = 10, 15, 25$.

(e) (2 points) **Graduate students** (bonus for undergraduates): What is the relationship between instability and oscillation. Why are some conditions unstable but not oscillatory?