Quasi-steady state approximation, Stability of a fixed point and its location on nullclines

Question 1:

1. The FitzHugh-Nagumo model is given by

\[
\begin{align*}
    x' &= f(x) - y, \quad (f(x) = I + x(x - \alpha)(1 - x), \; 0 < \alpha < 1/2), \\
    y' &= \epsilon(kx - y), \quad (\epsilon, \; k > 0).
\end{align*}
\]

Consider the case \( I = 0 \).

(a) At the limit \( \epsilon \to \infty \), use quasi-steady state approximation to study the behaviour of the system. Predict the long term behaviour of the system for different initial conditions for distinctive choices of \( k \) while \( \alpha \) is fixed.

(b) Write a .ode file that allows you to study the difference between the approximate system obtained in (a) and the original system for \( \epsilon = 1, 10, 100, 1000 \). (Use \( \alpha = 0.2 \) and \( k = 1 \), and initial condition \( x(0) = 1, \; y(0) = 0 \).) (Hint: Define the fast variable as a function of the slow one obtained in the quasi-steady state approximation as an aux variable in XPP. Then, plot it against the fast variable in the original system in comparison). Identify the difference between the two.

(c) If \( \alpha \) is a fixed parameter, find the value \( k = k_c \) at which a SN of steady state occurs (i.e., there is one s.s. for \( k > k_c \) and three for \( k < k_c \)).

(d) Sketch the nullclines of the system for \( k > k_c \).

Answer:

(a) Rewrite the second equation as follows and take the limit \( \epsilon \to \infty \),

\[
\epsilon^{-1} y' = kx - y \quad \epsilon \to \infty \quad 0 = kx - y \quad \Rightarrow \quad y = kx.
\]

Substitute into the first equation, we obtain

\[
x' = f(x) - kx = x[(x - \alpha)(1 - x) - k] = x[-x^2 + (1 + \alpha)x - (\alpha + k)].
\]

Possible steady states are \( x_s = 0 \) and that

\[
x_s^\pm = \frac{1 + \alpha}{2} \pm \sqrt{\left(\frac{1 + \alpha}{2}\right)^2 - (\alpha + k)}.
\]
which yields two new roots when
\[ \alpha + k < \left( \frac{1 + \alpha}{2} \right)^2 \Rightarrow k_c = \left( \frac{1 + \alpha}{2} \right)^2 - \alpha. \]

For \( k > k_c \), \( x_s = 0 \) is the only fixed point and is stable. So, the value of \( x \) will approach 0 irrespective of the initial value \( x(0) \).

For \( k = k_c \), one new fixed point emerges
\[ x^c_s = \frac{1 + \alpha}{2}. \]

It is semi-stable. For all \( x(0) \geq x^c_s \), \( x \) will approach \( x^c_s \) when \( t \to \infty \). In the mean time, \( x_s = 0 \) is always stable with a basin of attraction defined by \((-\infty, x^c_s)\). For all \( x(0) \) in this basin, \( x \) approaches 0 when \( t \to \infty \).

For \( k < k_c \), two new steady states exist
\[ x^\pm_s = \frac{1 + \alpha}{2} \pm \sqrt{\left( \frac{1 + \alpha}{2} \right)^2 - (\alpha + k)}. \]

such that \( 0 < x^-_s < x^+_s \) and that
\[ x' = -x(x - x^-_s)(x - x^+_s). \]

A simple sketch of the rhs of the equation above shows that 0 and \( x^+_s \) are stable while \( x^-_s \) is unstable. Thus, \( x^-_s \) is the separation point between the basins of attraction for the two stable steady states. For \( x(0) \) in \((-\infty, x^-_s)\), \( x \) will approach 0 as \( t \to \infty \). But for \( x(0) \) in \((x^-_s, \infty)\), \( x \) will approach \( x^+_s \) as \( t \to \infty \).

(b) Check the following graphs to see that for larger values of \( \epsilon \), the two agree really well except for a very short time interval between \( t = 0 \) and \( t = \Delta t \ll 1 \).

![Figure 1: Comparison in the phase space.](image)
Figure 2: Comparison as time series between $y(t)$ (black) and $kx(t)$ (yellow) for $\epsilon = 1, 10, 100, 1000$ respectively. Other parameter values: $\alpha = 0.2$, $k = 0.1$.

(c) The critical situation happens when the two nullclines are tangent to each other at the point $x = x^*$ and $k = k_c$. This is obtained by solving the following two equations

$$\begin{align*}
kx &= x(x - \alpha)(1 - x), \\
k &= -3x^2 + 2(1 + \alpha)x - \alpha.
\end{align*}$$

These equations yield $x^* = \frac{1+\alpha}{2}$ and $k_c = \frac{(1-\alpha)^2}{4}$.

(d) See the phase portrait in (b).

2. Now, consider the FitzHugh-Nagumo model for $I \neq 0$.

(a) Show that for $k > f'(1 + \alpha)/3 > k_c$, there is only one fixed point for changing values of $I$.

(b) Show that for $k > f'(1 + \alpha)/3 > k_c$, the determinant of $J(x_s, y_s)$ is always positive.

(c) Show that for $k > f'(1 + \alpha)/3 > k_c$, $f'(x_s) = \epsilon$ is a Hopf bifurcation which is only possible when $0 < \epsilon < f'(1 + \alpha)/3$.

(d) Show that for $k > f'(1 + \alpha)/3 > k_c$, the steady state is unstable if $f'(x_s) > \epsilon$ which is only possible when $0 < \epsilon < f'(1 + \alpha)/3$.

(e) Verify the results in (a)-(d) using XPP.

Answer:

(a) Since the effect of changing $I$ is to move the graph of $y = f(x)$ up vertically (for $I > 0$), so the two nullclines can intersect at any part of the $x$-nullcline. Notice that

$$f'(x) = -3x^2 + 2(1+\alpha)x - \alpha \quad \Rightarrow \quad f''(x) = -6x + 2(1+\alpha) = 0 \quad \Rightarrow \quad x_M = \frac{1+\alpha}{3}$$

is where the slope of $f(x)$ is the steepest (i.e. $f'(x)$ is the biggest). If $k > f'(x_M)$, then $y = kx$ is steeper than the steepest part of $y = I + f(x)$. So, the two can only cross once.
(b) The Jacobian is

\[ J(x_s) = \begin{bmatrix} f'(x_s) & -1 \\ \epsilon k & -\epsilon \end{bmatrix}. \]

Thus,

\[ Det = \epsilon(k - f'(x_s)) > 0, \quad \text{if} \quad k > f'(\frac{1+\alpha}{3}) = \max \{ f'(x) : \text{for all } x \}. \]

(c) Result in (b) shows that if \( k > f'((1+\alpha)/3) > k_c \), \( Det > 0 \) is guaranteed. Under this condition, instability can only occur when \( Tr = 0 \) where the real part of a pair of complex eigenvalues change sign. Since

\[ Tr = f'(x_s) - \epsilon = 0 \quad \Rightarrow \quad f'(x_s) = \epsilon. \]

However, if \( \epsilon > f'(\frac{1+\alpha}{3}) \), \( Tr = f'(x_s) - \epsilon < 0 \) must always to be true. Thus, \( Tr \) cannot change sign. If \( \epsilon = f'(\frac{1+\alpha}{3}) \), then \( Tr = 0 \) for \( x_s = \frac{1+\alpha}{3} \). But it can never be positive.

(d) Result in (b) shows that if \( k > f'((1+\alpha)/3) > k_c \), \( Det > 0 \) is guaranteed. Under this condition, instability of the steady state is possible only if

\[ Tr = f'(x_s) - \epsilon > 0 \quad \Rightarrow \quad f'(x_s) > \epsilon. \]

It is obvious that the above condition is only possible if \( \epsilon < f'((1+\alpha)/3) = \max \{ f'(x) : \text{for all } x \} \).

(e) Notice that

\[ f'(x_M) = -3x_M^2 + 2(1+\alpha)x_M - \alpha - (1+\alpha)^2/3 + 2(1+\alpha)^2/3 - \alpha = (1+\alpha)^2/3 - \alpha. \]

For \( \alpha = 0.2 \), \( f'(x_M) = f'(\frac{1+\alpha}{3}) = 0.28 \). Now, let us use two distinct values of \( k \) to show the difference: \( k_1 = 0.5 > f'(\frac{1+\alpha}{3}) \) and \( k_2 = 0.1 < f'(\frac{1+\alpha}{3}) \).
Figure 3: Bifurcation diagrams against $I$ for $k = k_1 = 0.5$ (left) where the two bifurcation points are HBs and for $k = k_2 = 0.1$ (right) where the two bifurcation points are SNs. In the latter case, we get three steady states for values of $I$ around zero. The points where colour changes are bifurcation points. Red represents stable fixed points while black stands for unstable ones. Other parameter values: $\alpha = 0.2$, $\epsilon = 0.1$.

Figure 4: Phase diagrams. For $k = k_1 = 0.5$ and $I = 0.155$ (left), the fixed point in the middle is an unstable spiral with eigenvalues $0.089713 \pm i(0.118360)$. A spiral is possible only when the determinant of the Jacobian is positive at that point. For $k = k_2 = 0.1$ and $I = -0.01$ (right), the fixed point at the centre is a saddle node with eigenvalues $0.251136$ and $-0.071521$. This is possible only when the determinant of the Jacobian is negative at that point.
Figure 5: The same bifurcation diagram as obtained in Fig. 3 (left) is computed now for $\epsilon = 0.3 > f'(x_M) = 0.28$ but not for $\epsilon = 0.1$. Now, instability is not possible. There is neither HB point nor unstable steady state.
Question 2:

Consider the following form of FitzHugh-Nagumo equation

\[
\begin{align*}
\dot{x} &= f(x) - y, \\
\dot{y} &= \epsilon(x + a),
\end{align*}
\]

where \( f(x) = x - x^3/3, 0 < \epsilon \leq 1 \) and \( a \) are parameters.

(a) Show that the steady state \((x_s, y_s) = (-a, f(-a))\) is stable if \( f'(x) < 0 \) at the fixed point. It is unstable if \( f'(-a) > 0 \). Show that \( f'(x) = 0 \) at \( x = \pm 1 \) which happens when \( a = \mp 1 \). Both are Hopf bifurcation points.

(b) Use XPP to demonstrate that for \( a \) values slightly larger than 1, the system is more excitable as the value of \( \epsilon \) decreases. The degree of excitability can be determined by the amplitude of the response of the system to stimuli that are above threshold.

(c) Use XPPAUT to draw the bifurcation diagrams against parameter \( a \) for three different values of \( \epsilon \): 1, 0.1, 0.01. Draw both the steady state and oscillatory branches of the solutions.

Solution:

(a) (i) \( f'(x) = r - 4x - 3x^2 \). \( f'(0) = r \). Thus, for \( r < 0 \) it is stable and for \( r > 0 \) it is unstable. (ii) Note that \( f(0, 0) = 0, f_x(0, 0) = 0, f_{xr}(0, 0) = 1 \) and \( f_{xx}(0, 0) = -4 \), it is a TC bifurcation point.

(b) (i) \( f(x) = x(r - 2x - x^2) = 0 \) yields \( x_s = 0 \) and \( x_s = -1 \pm \sqrt{1 + r} \), the latter two exist only when \( r > -1 \). (ii) See Fig. 1(b)(ii). (iii) See Fig. 1(b)(iii).

(Fig. 1b(ii))
(Fig. 1b(iii))

(c) See Fig. 1(c).

(Fig. 1c)
Question 3:

In the glycolytic oscillator model,

\[
S = F6P + ATP; \quad P = FBP + ADP.
\]

Pye et al (1971) extract of yeast cells

Letter \( S \) denotes the substrate of the reaction, \( P \) represents the product. We assume that the allosteric enzyme \( E \) has 2 identical subunits and that the enzyme in R (relaxed) state binds to \( S \) and \( P \) but not the T (tense) state. Monod-Wyman-Changeux model (Monod, J., Wyman, J, Changeux, J.P. On the nature of allosteric transitions: a plausible model. *J Mol Biol.* 12:88-118, 1965) leads to the following system of ODEs

\[
\frac{ds}{d\tau} = v - \phi(s, p), \quad \left( \phi = \frac{\sigma s(1 + s)}{L/(1 + p)^2 + (1 + s)^2} \right),
\]

\[
\frac{dp}{d\tau} = \epsilon^{-1}\phi(s, p) - p,
\]

(2)

where \( s = [S]/K_S \), \( p = [P]/K_P \), \( \tau = kt \), \( v = V/(kK_S) \), \( \sigma = 2k[E]T/(kK_S) \), \( \epsilon = K_P/K_S \), \( L = k_1/k_2 \) are all positive dimensionless.

Here are the assignments:

(a) The nullclines of this system are plotted in the figure given below. Show that the steady state is unstable only when it is located on the part of \( p' = 0 \) nullcline where the slope satisfies

\[
\frac{ds}{dp}_{p'=0} < -\epsilon.
\]

That is, it is unstable only when the slope is more negative than \(-\epsilon\).

(b) Explain why the specific functional form of \( \phi(s, p) \) is not important for the previous result to hold as long as it generates the \( N \)–shaped nullcline in the fast variable and the monotonic nullcline in the slow variable and that: \( \frac{\partial\phi}{\partial s} > 0 \) and \( \frac{\partial\phi}{\partial p} > 0 \) for all \( s, p > 0 \).
Solution:

(a) The steady state is given by \((s_s, p_s) = (s_s, v/\epsilon)\) where \(x_s\) is a solution of \(v = \phi(s_s, v/\epsilon)\).

\[
J(s_s, p_s) = \begin{bmatrix}
-\phi_s(s_s, p_s) & -\phi_p(s_s, p_s) \\
\epsilon^{-1}\phi_s(s_s, p_s) & \epsilon^{-1}\phi_p(s_s, p_s) - 1
\end{bmatrix}.
\]

Thus, \(\text{Det} = \phi_s(s_s, p_s)\) and that \(\text{Tr} = \epsilon^{-1}\phi_p(s_s, p_s) - \phi_s(s_s, p_s) - 1\).

It is obvious that for the expression of \(\phi(s, p)\) given in the question, \(\phi_s(s_s, p_s) > 0\) for all \(s_s, p_s > 0\). Therefore, instability is totally determined by the sign of the trace:

\[
\text{Tr} = \epsilon^{-1}\phi_p(s_s, p_s) - \phi_s(s_s, p_s) - 1 > 0 \quad \Rightarrow \quad -\epsilon\phi_s(s_s, p_s) > \epsilon - \phi_p(s_s, p_s),
\]

which, combined with the fact that \(\phi_s(s_s, p_s) > 0\) implies that

\[
\frac{\epsilon - \phi_p(s_s, p_s)}{\phi_s(s_s, p_s)} < -\epsilon.
\]

Notice that the fast nullcline is defined by

\[
\phi(s, p) - \epsilon p = 0.
\]

Differentiate both sides w.r.t. \(p\);

\[
\phi_s \frac{ds}{dp} + \phi_p - \epsilon = 0 \quad \Rightarrow \quad \frac{ds}{dp}_{p'=0} = \frac{\epsilon - \phi_p}{\phi_s}_{p'=0}.
\]

Therefore, if \((s_s, p_s)\) is located on the fast nullcline \(p' = 0\) where

\[
\frac{ds}{dp}_{p'=0} = \frac{\epsilon - \phi_p}{\phi_s}_{p'=0} < -\epsilon,
\]

then, \(\text{Tr} > 0\) is guaranteed.

It is obvious from this condition, given that \(\epsilon, \phi_s > 0, \phi_p > 0\) is a necessary condition for this to happen.
(b) It is obvious from the derivation that the only conditions used in the derivation were

\[ \phi_s(s_s, p_s), \phi_p(s_s, p_s) > 0, \]

and that \( \epsilon \) is small enough so that \( \phi_p(s_s, p_s) > \epsilon \) can be realized and that the slope of the fast nullcline can be more negative than \(-\epsilon\) at the steady state. All other conditions are not necessary.