ACM41000: Uncertainty Quantification

Assignment 3

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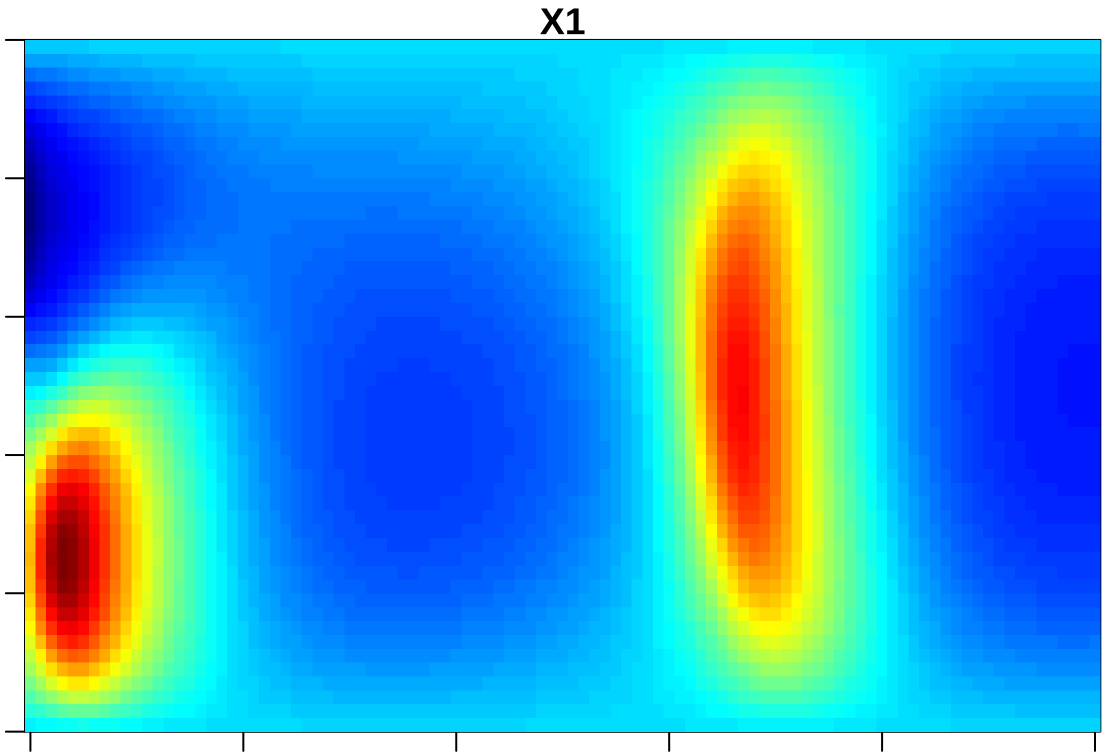
Question 1

(a)

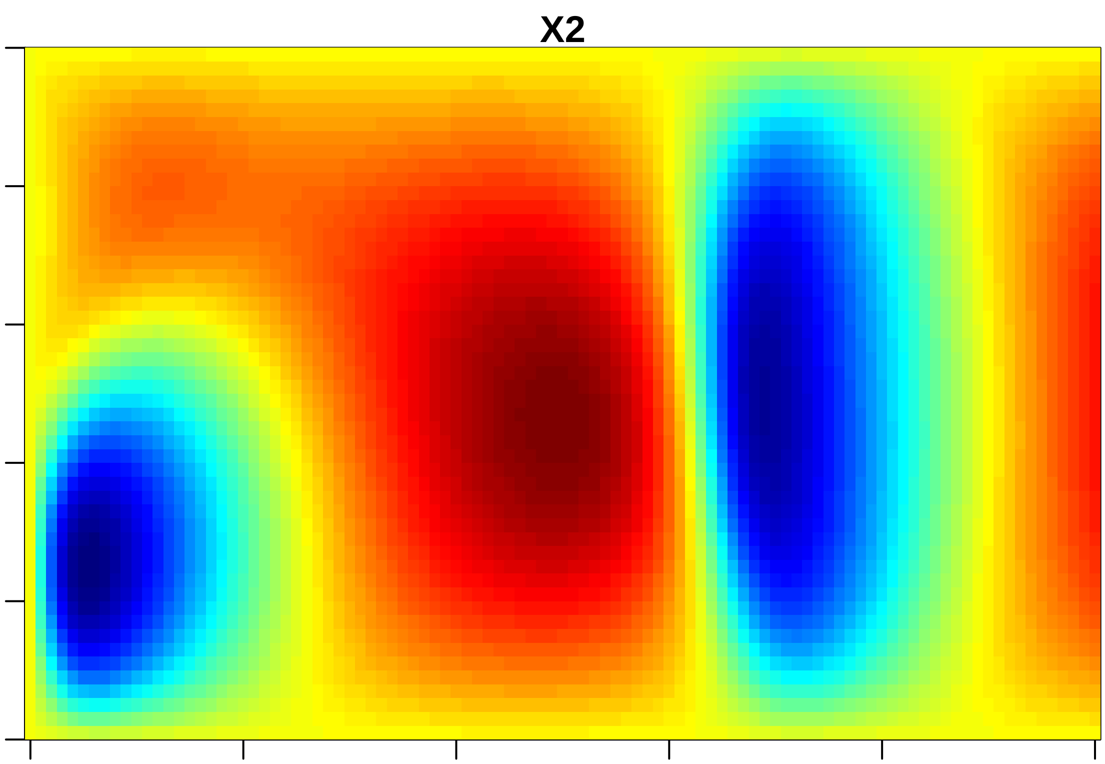
```
######## Question 1 ########

library(ReacTran)
library(deSolve)
library(reshape2)
library(minpack.lm)

# discretize x variables for method of lines
N    <- 50
Grid <- setup.grid.1D(x.up = 0, x.down = 1, N = N)

# initial values
x1ini <- 1 + sin(2 * pi * Grid$x.mid)
x2ini <- rep(x = 3, times = N)
yini <- c(x1ini, x2ini)

#set diffusion constants
D1 = D2 = 0.02

# function that extracts how the diffusion eqn is written
# correct form of PDE
fn <- function(t, y, parms) {

  X1 <- y[1:N]
  X2 <- y[(N+1):(2*N)]

  # dX1 and dX2 as per (a)
  # dX1
  dX1 <- tran.1D(C = X1,  C.up =  1, C.down = 1, D = D1, dx = Grid)$dC + #second order equation of X1 wrt
    1 + (X1^2)*X2 - 4*X1    # other terms
  # dx2
  dX2 <- tran.1D(C = X2,  C.up =  3, C.down = 3,D = D2, dx = Grid)$dC + #second order equation of X2 wrt x
    3*X1 - (X1^2)*X2 # other terms

  list(c(dX1, dX2))  # return results
}

# set times
times <- seq(from = 0, to = 10, by = 0.1)

# fit pde & print run time
print(system.time(
  out <- ode.1D(y = yini, func = fn,
                times = times, parms = NULL, nspec = 2,
                names = c("X1", "X2"), dimens = N)
))
```

```
##    user  system elapsed
##    0.05    0.01    0.08
```

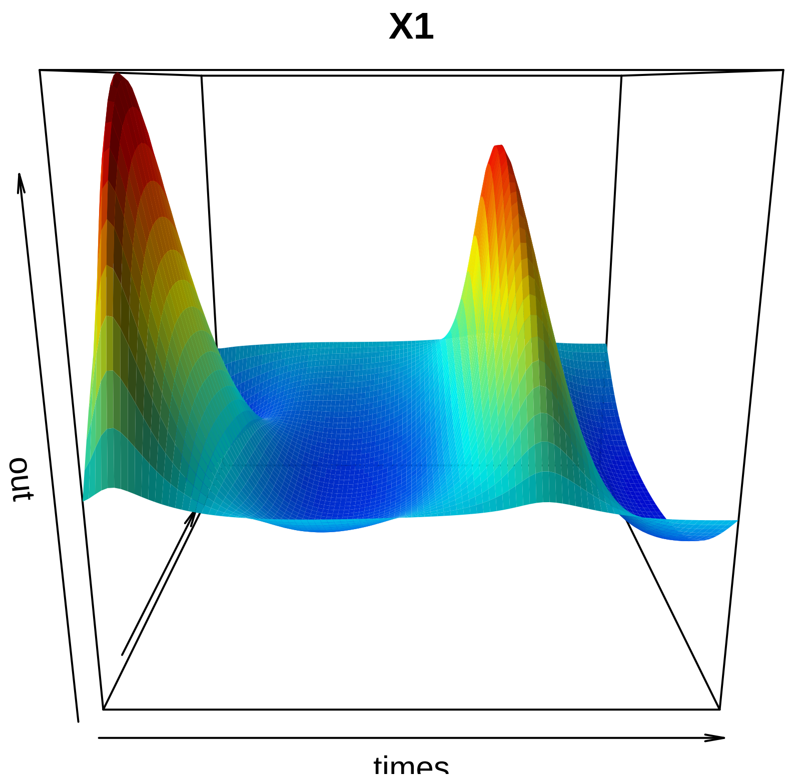
```
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid,which = "X1")
```



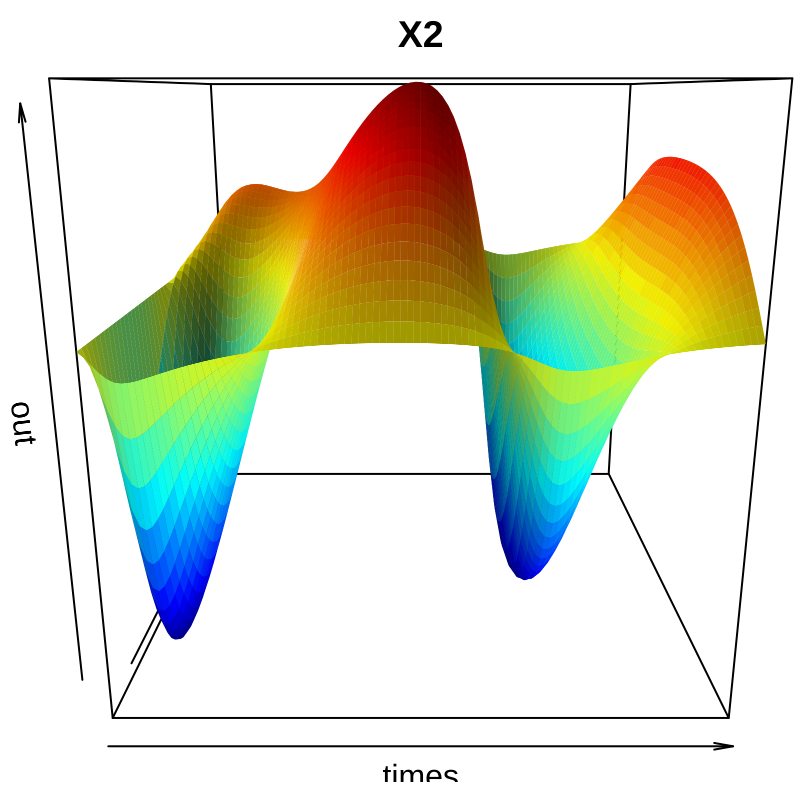

```
image(out, mfrow = NULL, grid = Grid$x.mid, which = "X2")
```



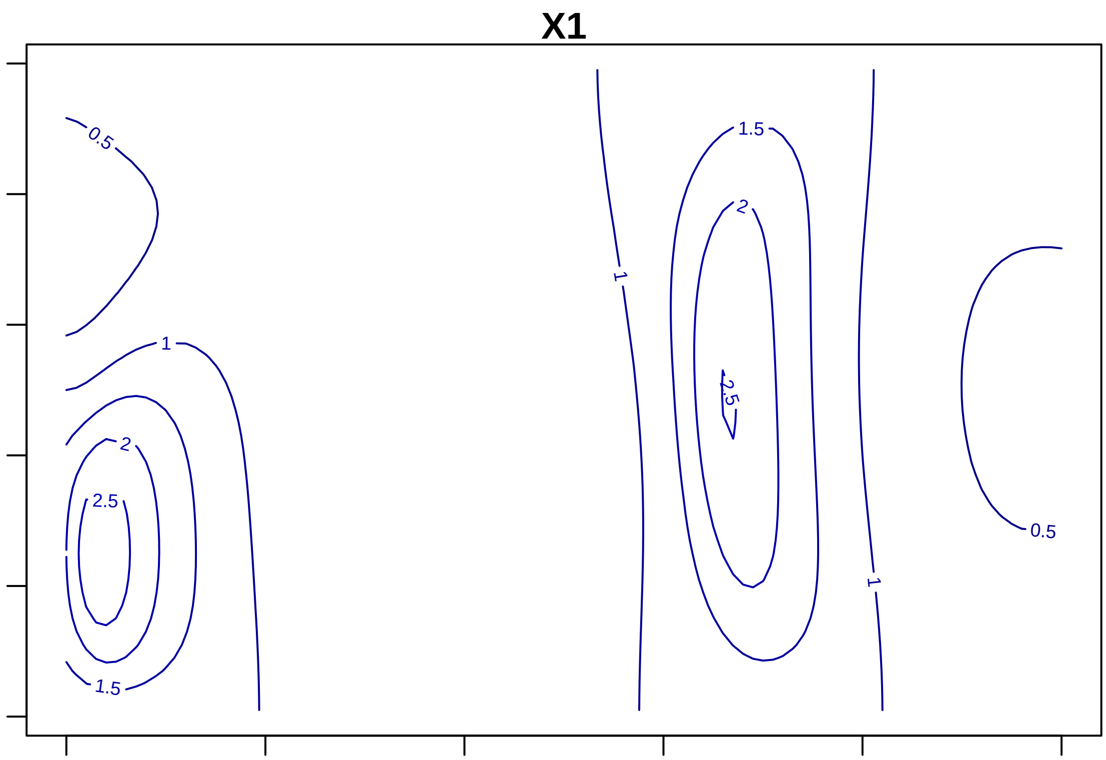
```
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid,  which = "X1", method = "persp", border = NA, shade = 0.3 )
```



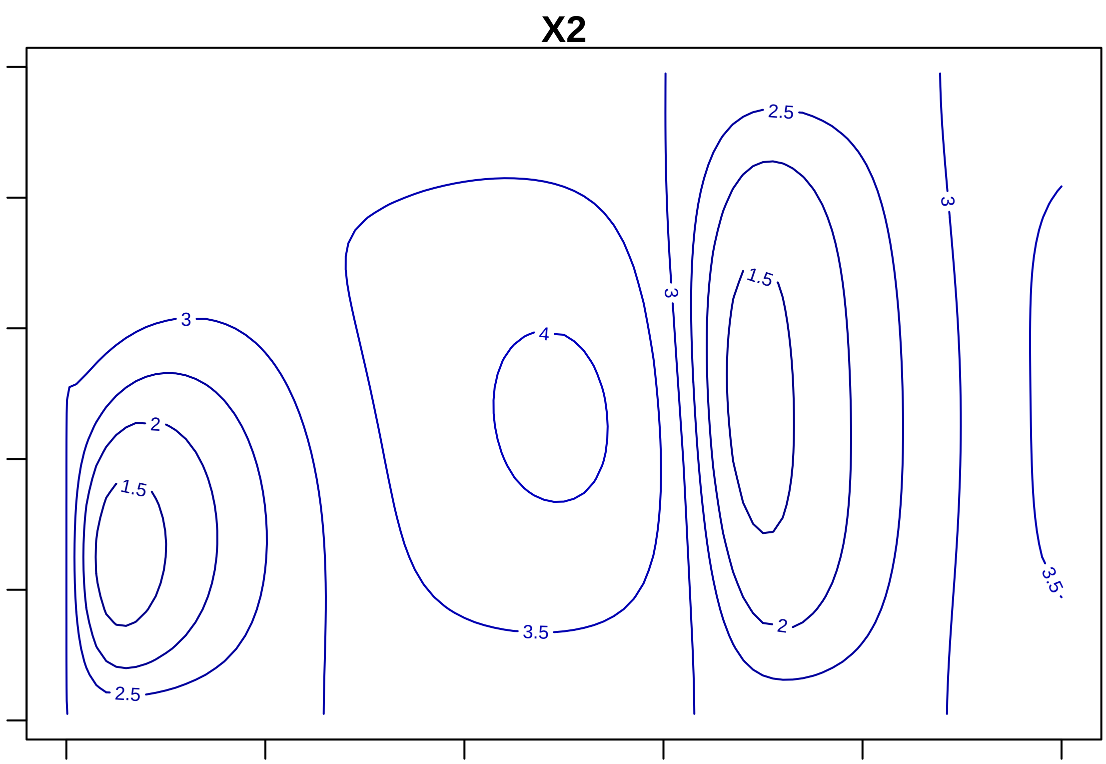

```
image(out, mfrow = NULL, grid = Grid$x.mid,   which = "X2",  method = "persp", border = NA, shade = 0.3 )
```



```
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid,   which = "X1",  method = "contour", border = NA, shade = 0.3
```




```
image(out, mfrow = NULL, grid = Grid$x.mid, which = "X2",  method = "contour", border = NA, shade = 0.3 )
```



(b)

The sensitivity equations were derived to be

$$\frac{\partial S_{11}}{\partial t} = \frac{\partial^2 X_1}{\partial x^2} + D_1 \frac{\partial^2 S_{11}}{\partial x^2} + S_{11}(2X_1X_2 - 4) + S_{21}X_1^2$$

$$\frac{\partial S_{12}}{\partial t} = D_1 \frac{\partial^2 S_{12}}{\partial x^2} + S_{12}(2X_1X_2 - 4) + S_{22}X_1^2$$

$$\frac{\partial S_{21}}{\partial t} = D_2 \frac{\partial^2 S_{21}}{\partial x^2} + S_{11}(3 - 2X_1X_2) - S_{21}X_1^2$$

$$\frac{\partial S_{22}}{\partial t} = \frac{\partial^2 X_2}{\partial x^2} + D_2 \frac{\partial^2 S_{22}}{\partial x^2} + S_{12}(3 - 2X_1X_2) - S_{22}X_1^2$$

Derivations over next two pages

$$\frac{\partial X_1}{\partial t} = D_1 \frac{\partial^2 X_1}{\partial x^2} + 1 + X_1^2 X_2 - 4X_1$$

① $$S_{11} = \frac{\partial X_1}{\partial D_1} \; ; \; \frac{\partial S_{11}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial X_1}{\partial D_1}\right) = \frac{\partial}{\partial D_1}\left(\frac{\partial X_1}{\partial t}\right)$$

$$\Rightarrow \frac{\partial S_{11}}{\partial t} = \frac{\partial}{\partial D_1}\left(D_1 \frac{\partial^2 X_1}{\partial x^2} + 1 + X_1^2 X_2 - 4X_1 \right)$$

$$= \frac{\partial^2 X_1}{\partial x^2} + D_1 \frac{\partial}{\partial D_1}\left(\frac{\partial^2 X_1}{\partial^2 x_2}\right) + X_2 \frac{\partial (X_1^2)}{\partial D_1} + X_1^2 \frac{\partial X_2}{\partial \cancel{D_1}} - 4 \frac{\partial X_1}{\partial D_1}$$

$$= \frac{\partial^2 X_1}{\partial x^2} + D_1 \frac{\partial^2 S_{11}}{\partial x^2} + 2X_2 X_1 \overset{S_{11}}{\frac{\partial X_1}{\partial D_1}} + X_1^2 S_{21} - 4 S_{11}$$

$$= \frac{\partial^2 X_1}{\partial x^2} + D_1 \frac{\partial^2 S_{11}}{\partial x^2} + S_{11}(2X_1 X_2 - 4) + S_{21} X_1^2$$

② $$S_{12} = \frac{\partial X_1}{\partial D_2} \; ; \; \frac{\partial S_{12}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial X_1}{\partial D_2}\right) = \frac{\partial}{\partial D_2}\left(\frac{\partial X_1}{\partial t}\right)$$

$$\Rightarrow \frac{\partial S_{12}}{\partial t} = \frac{\partial}{D_2}\left(D_1 \frac{\partial^2 X_1}{\partial x^2} + 1 + X_1^2 X_2 - 4X_1 \right)$$

$$= D_1 \frac{\partial}{\partial D_2}\left(\frac{\partial^2 X_1}{\partial x^2}\right) + X_2 \frac{\partial}{\partial D_2}(X_1^2) + X_1^2 \frac{\partial X_2}{\partial D_2} - 4 \frac{\partial X_1}{\partial D_2}$$

$$= D_1 \frac{\partial^2}{\partial x^2} \frac{\partial X_1}{\partial D_2} + X_2\, 2X_1 \frac{\partial X_1}{\partial D_2} + X_1^2 \frac{\partial X_2}{\partial D_2} - 4\frac{\partial X_1}{\partial D_2}$$

$$= D_1 \frac{\partial^2 S_{12}}{\partial x^2} + 2X_1 X_2 S_{12} + X_1^2 S_{22} - 4 S_{12}$$

$$= D_1 \frac{\partial^2 S_{12}}{\partial x^2} + S_{12}(2X_{12} X_2 - 4) + S_{22} X_1^2$$

$$\partial X_2 = D_2 \frac{\partial^2 X_2}{\partial x^2} + 3X_1 - X_1^2 X_2$$

③ $S_{21} = \frac{\partial X_2}{\partial D_1}$; $\frac{\partial S_{21}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial X_2}{\partial D_1}\right) = \frac{\partial}{\partial D_1}\left(\frac{\partial X_2}{\partial t}\right)$

$$\frac{\partial S_{21}}{\partial t} = \frac{\partial}{\partial D_1}\left(D_2 \frac{\partial^2 X_2}{\partial x^2} + 3X_1 - X_1^2 X_2 \right)$$

$$= D_2 \frac{\partial}{\partial D_1}\left(\frac{\partial^2 X_2}{\partial x^2}\right) + 3\frac{\partial X_1}{\partial D_1} - X_2 \frac{\partial (X_1^2)}{\partial D_1} - X_1^2 \frac{\partial X_2}{\partial D_1}$$

$$= D_2 \frac{\partial^2 S_{21}}{\partial x^2} + 3S_{11} - X_2\, 2X_1 S_{11} - X_1^2 S_{21}$$

$$= D_2 \frac{\partial^2 S_{21}}{\partial x^2} + S_{11}(3 - 2X_2 X_1) - S_{21} X_1^2$$

④ $S_{22} = \frac{\partial X_2}{\partial D_2}$; $\frac{\partial S_{22}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial X_2}{\partial D_2}\right) = \frac{\partial}{\partial D_2}\left(\frac{\partial X_2}{\partial t}\right)$

$$\frac{\partial S_{22}}{\partial t} = \frac{\partial}{\partial D_2}\left(D_2 \frac{\partial^2 X_2}{\partial x^2} + 3X_1 - X_1^2 X_2 \right)$$

$$= \frac{\partial^2 X_2}{\partial x^2} + D_2 \frac{\partial}{\partial D_2}\frac{\partial^2 X_2}{\partial x^2} + 3\frac{\partial X_1}{\partial D_2} - X_2 \frac{\partial (X_1^2)}{\partial D_2} - X_1^2 \frac{\partial X_2}{\partial D_2}$$

$$= \frac{\partial^2 X_2}{\partial x^2} + D_2 \frac{\partial^2 S_{22}}{\partial x^2} + 3S_{12} - X_2\, 2X_1 S_{12} - X_1^2 S_{22}$$

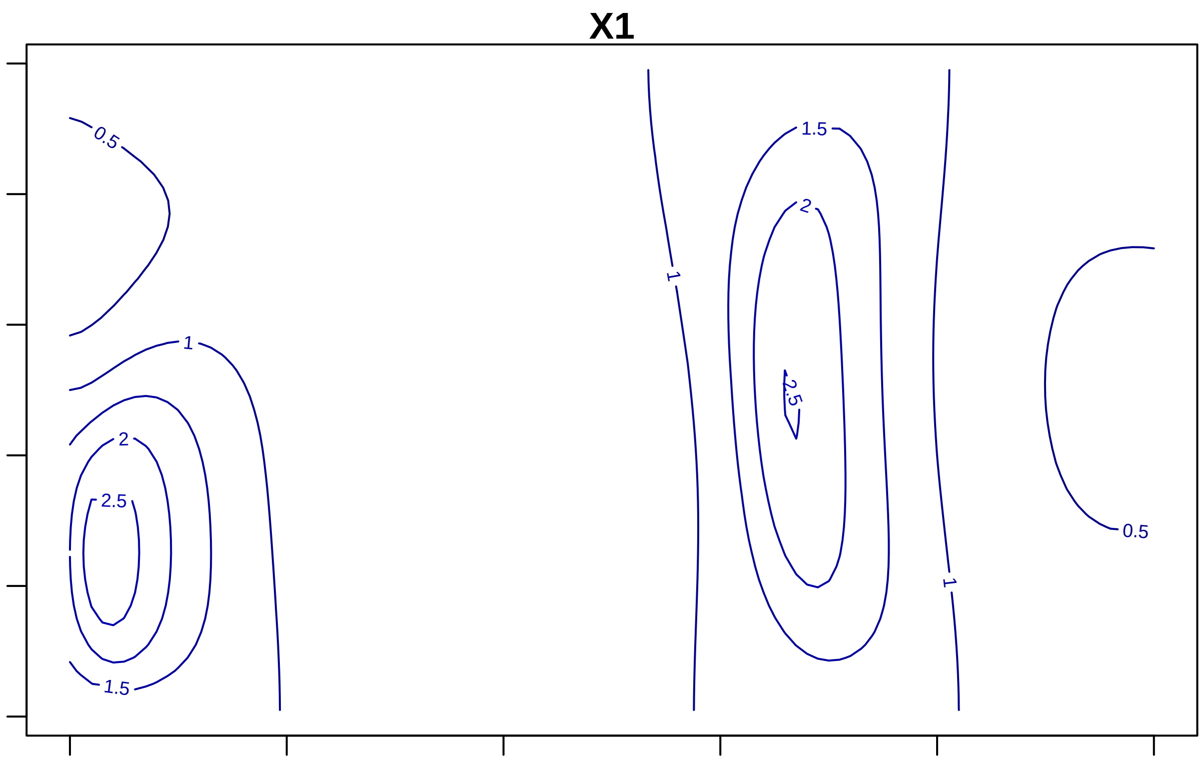
$$= \frac{\partial^2 X_2}{\partial x^2} + D_2 \frac{\partial^2 S_{22}}{\partial x^2} + S_{12}(3 - 2X_1 X_2) - X_1^2 S_{22}$$

(c)

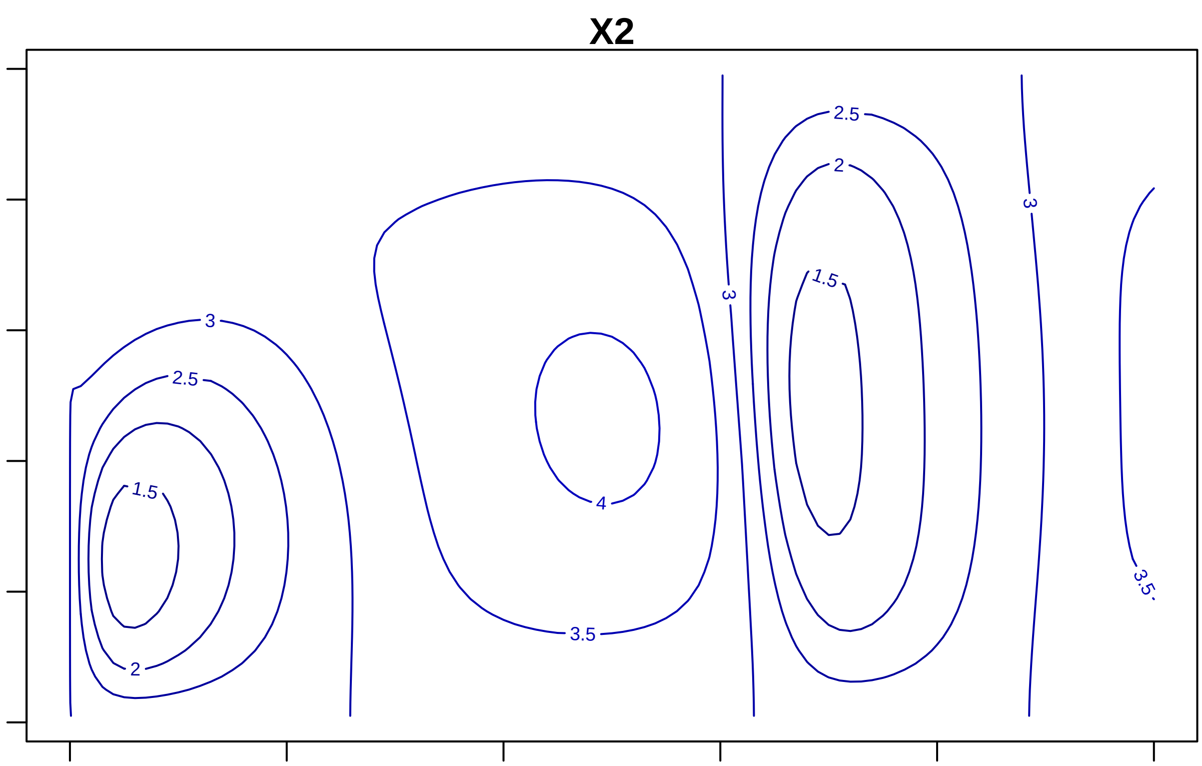
```
# initial conditions
x1ini <- 1 + sin(2 * pi * Grid$x.mid)
x2ini <- rep(x = 3, times = N)
s11ini <- rep(x = 0, times = N)
s12ini <- rep(x = 0, times = N)
s21ini <- rep(x = 0, times = N)
s22ini <- rep(x = 0, times = N)
yini <- c(x1ini, x2ini,s11ini,s12ini,s21ini,s22ini)

fnsens <- function(t, y, parms) {
  # range of iteration
  X1 <- y[1:N]
  X2 <- y[(N+1):(2*N)]
  s11 <- y[(2*N+1):(3*N)]
  s12 <- y[(3*N+1):(4*N)]
  s21 <- y[(4*N+1):(5*N)]
  s22 <- y[(5*N+1):(6*N)]

  # dX1 and dX2 as per (a)
  # dX1
  dX1 <- tran.1D(C = X1,  C.up =  1, C.down = 1,D = D1, dx = Grid)$dC +
    1 + (X1^2)*X2 - 4*X1
  # dX2
  dX2 <- tran.1D(C = X2,  C.up =  3, C.down = 3,D = D2, dx = Grid)$dC +
    3*X1 - (X1^2)*X2

  # ds11, ds12, ds21 and ds22 as per derivations in (b)
  # ds11
  ds11 <-  tran.1D(C = X1,  C.up =  1, C.down = 1,D=1, dx = Grid)$dC + # X1 derivative
    tran.1D(C = s11,  C.up =  0, C.down = 0, D = D1, dx = Grid)$dC +  # S11 derivative
    s11*((2*X1*X2) - 4) + s21*(X1^2) # remaining terms
  # ds12
  ds12 <- tran.1D(C = s12,  C.up =  0, C.down = 0, D = D1, dx = Grid)$dC +  # S12 derivative
    s12*((2*X1*X2) - 4) + s22*(X1^2) # remaining terms
  # ds21
  ds21 <- tran.1D(C = s21,D = D2,  C.up =  0, C.down = 0, dx = Grid)$dC + # S21 derivative
    s11*(3 - (2*X1*X2)) - s21*(X1^2) # remaining terms
  # ds22
  ds22 <- tran.1D(C = X2, C.up =  3, C.down = 3, D=1, dx = Grid)$dC + # X2 derivative
    tran.1D(C = s22,  C.up =  0, C.down = 0, D = D2, dx = Grid)$dC + # S22 derivative
    s12*(3 - (2*X1*X2)) - s22*(X1^2) # remaining terms

  #return list
  list(c(dX1, dX2, ds11, ds12, ds21, ds22))
}

# range of times as per given code
times <- seq(from = 0, to = 10, by = 0.1)

print(system.time(
  out <- ode.1D(y = yini, func = fnsens, times = times, parms = NULL, nspec = 6,
                names = c("X1", "X2","s11","s12","s21","s22"), dimens = N)
))
```

```
##    user  system elapsed
##    2.31    0.00    2.33
```

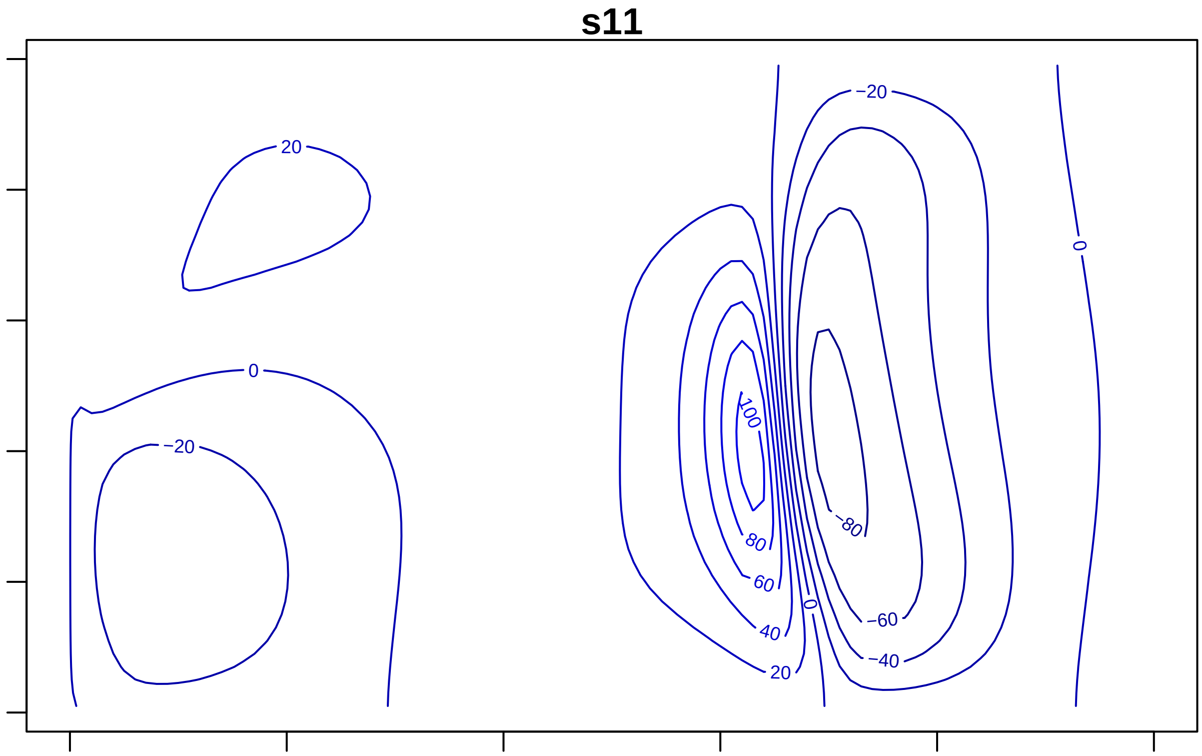
```
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid,which = "X1",  method = "contour", border = NA, shade = 0.3)
```



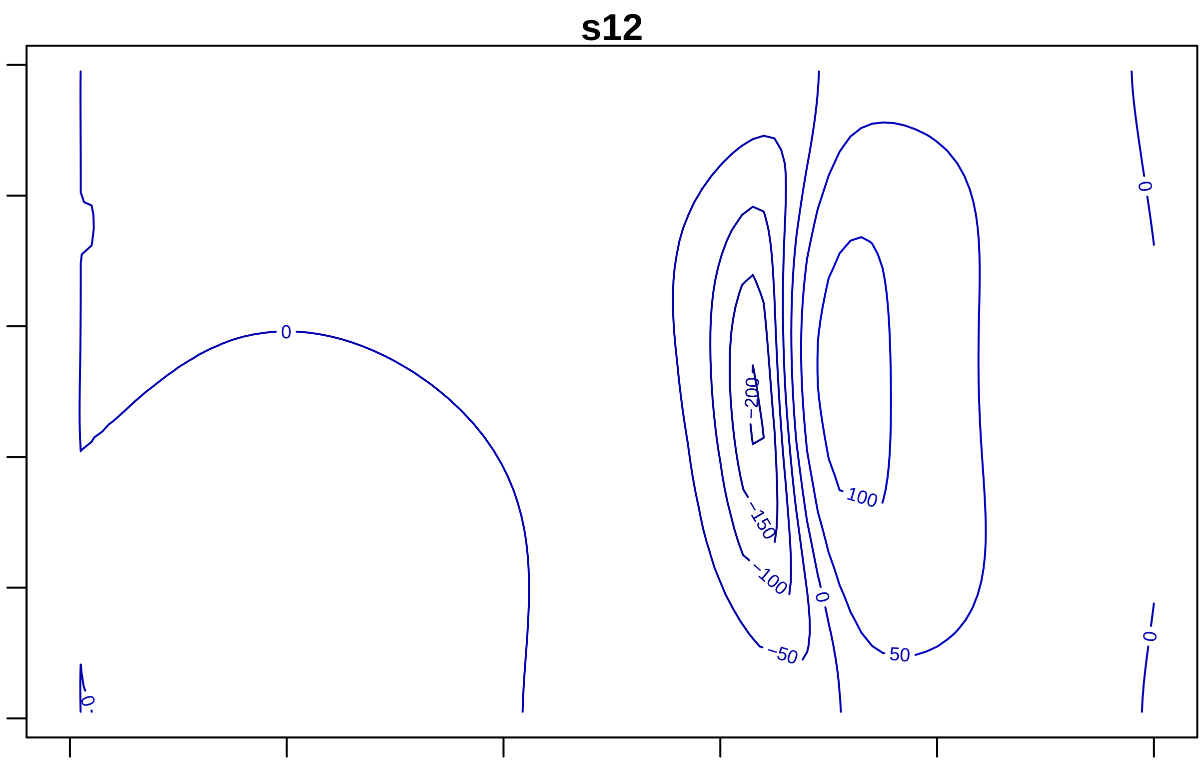

```
image(out, mfrow = NULL, grid = Grid$x.mid,which = "X2",  method = "contour", border = NA, shade = 0.3)
```



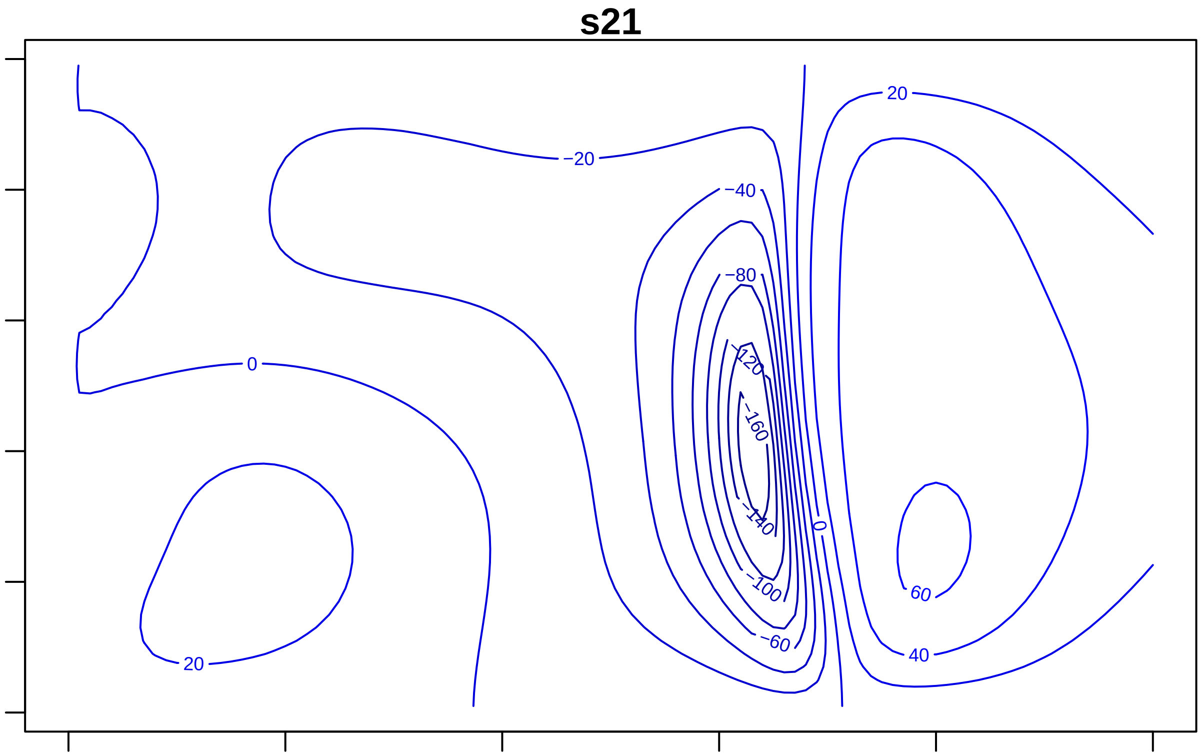
```r
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid, which = "s11",  method = "contour", border = NA,shade = 0.3)
```



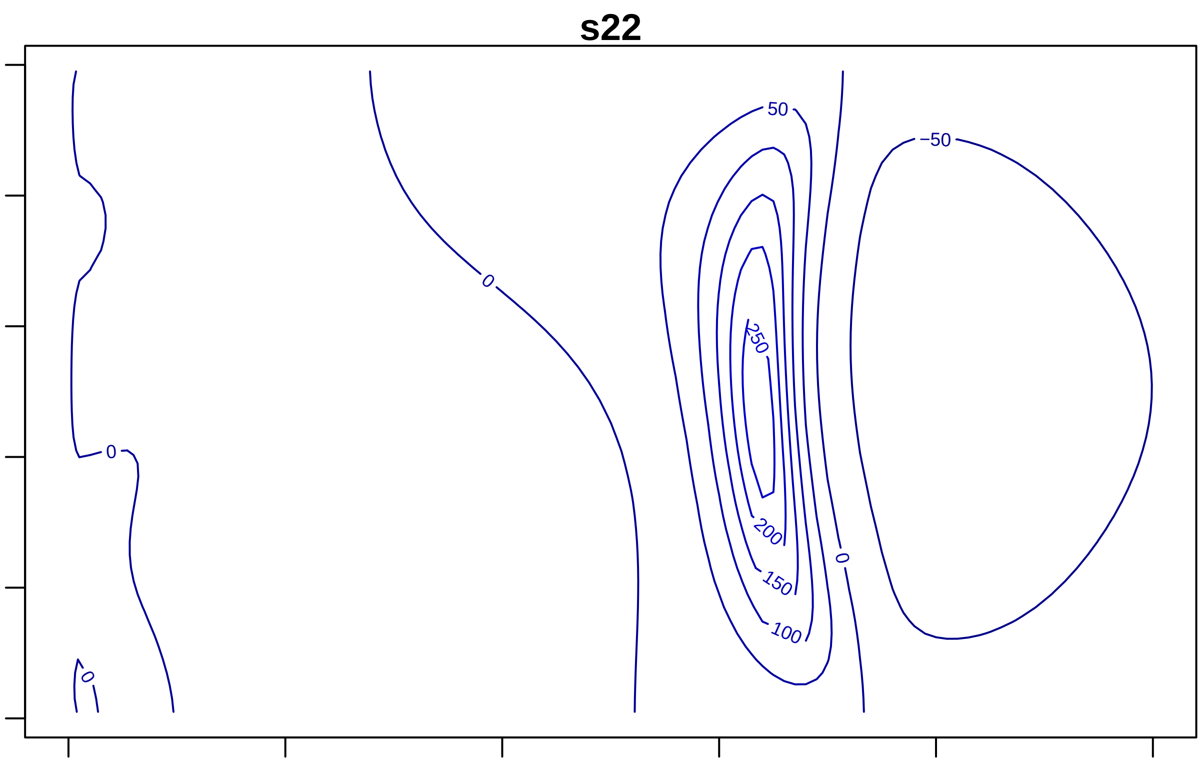

```r
image(out, mfrow = NULL, grid = Grid$x.mid, which = "s12",  method = "contour", border = NA,shade = 0.3)
```



```
par(mar = c(1, 1, 1, 1))
image(out, mfrow = NULL, grid = Grid$x.mid,which = "s21",   method = "contour", border = NA,shade = 0.3)
```




```
image(out, mfrow = NULL, grid = Grid$x.mid,which = "s22",   method = "contour", border = NA,shade = 0.3)
```



```r
summary(out, which = c("s11","s12","s21","s22"))
```

```
##                s11          s12          s21        s22
## Min.     -89.017441 -206.9216224 -179.6012155 -80.266675
## 1st Qu.  -14.529417   -7.8505084  -17.0733473 -21.153546
## Median     2.497789    0.8003933    0.7488599  -8.587284
## Mean      -2.362759    3.9791812    0.1643025  -2.946001
## 3rd Qu.   12.174637   17.7872417   24.5009486   2.233219
## Max.     111.838265  117.7781142   63.6866566 287.467696
## N       5050.000000 5050.0000000 5050.0000000 5050.000000
## sd        28.354016   43.4253187   37.2496212  54.445093
```

(d)

$$S_{11} = \frac{\partial X_1}{\partial D_1}$$

The sensitivity of X_1 to D_1 is largely stable in the range of (-20,20) over the first half of the time sequence. Following that however it becomes far more volatile, peaking and subsequently plummeting with sensitivities ranging of -89 to 111 approx.

$$S_{12} = \frac{\partial X_1}{\partial D_1}$$

X_1 is less sensitive to D_2 than it is to D_1 over the first half of the time sequence where it is in the range of (0,20) . However it is far more sensitive to D_2 after this, plummeting and subsequently peaking with sensitivities ranging of -200 to 117 approx.

$$S_{21} = \frac{\partial X_2}{\partial D_2}$$

The sensitivity of X_2 to D_1 is largely stable in the range of (-20,20) over the first half of the time sequence. Following that however it becomes far more volatile, plummeting and subsequently peaking with sensitivities ranging of -179 to 63 approx.

$$S_{22} = \frac{\partial X_2}{\partial D_2}$$

X_2 is less sensitive to D_2 than it is to D_1 over the first half of the time sequence where it is in the range of (0,20) . However it is far more sensitive to D_2 after this, peaking and subsequently plummeting with sensitivities ranging of -80 to 287 approx.

In summary, both X_1 and X_2 are more sensitive to D_2 than they are to D_1. All four sensitivity equations follow a similar pattern but the scale of $S12$ and $S22$ is far in excess of $S11$ and $S21$.

Question 2

(a)

The model described in (3.10) is in relation to biochemical data models for the concentration of dimers - a molecule or molecular complex consisting of two identical molecules linked together - in the context of their reaction rates with monomers.

The various dimer concentrations are denoted by x, y, z respectively and modelled by the following differential equations:

$$\frac{\partial x}{\partial t} = k_+(2d_{11} + d_{12} - 2x - z)^2 - k_- x$$

$$\frac{\partial y}{\partial t} = k_+(2d_{22} + d_{12} - 2y - z)^2 - k_- y$$

$$\frac{\partial y}{\partial t} = 2k_+(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) - k_- z$$

x is the concentration of regular dimer (D_{11}), y is the concentration of Fusion Dimer (D_{22}) and z is the concentration of Heterodimer (D_{12}).

d_{11}, d_{22} and d_{12} are the initial conditions, the values for the concentration of the dimers at time $t = t_0$ i.e. $x(t_0) = d_{11}$, $y(t_0) = d_{22}$ and $z(t_0) = d_{12}$. Limitations of the experimental process make it impossible to record data before two minutes, i.e., 1/30 hours. From the experimental data (Appendix A.), dimer concentrations have initial recordings in the range of 1.52 - 1.88 for D_{11}, 1.75-2.25 for D_{22} and 0.16 - 0.62 for D_{12}. All concentrations are measured in micromolars.

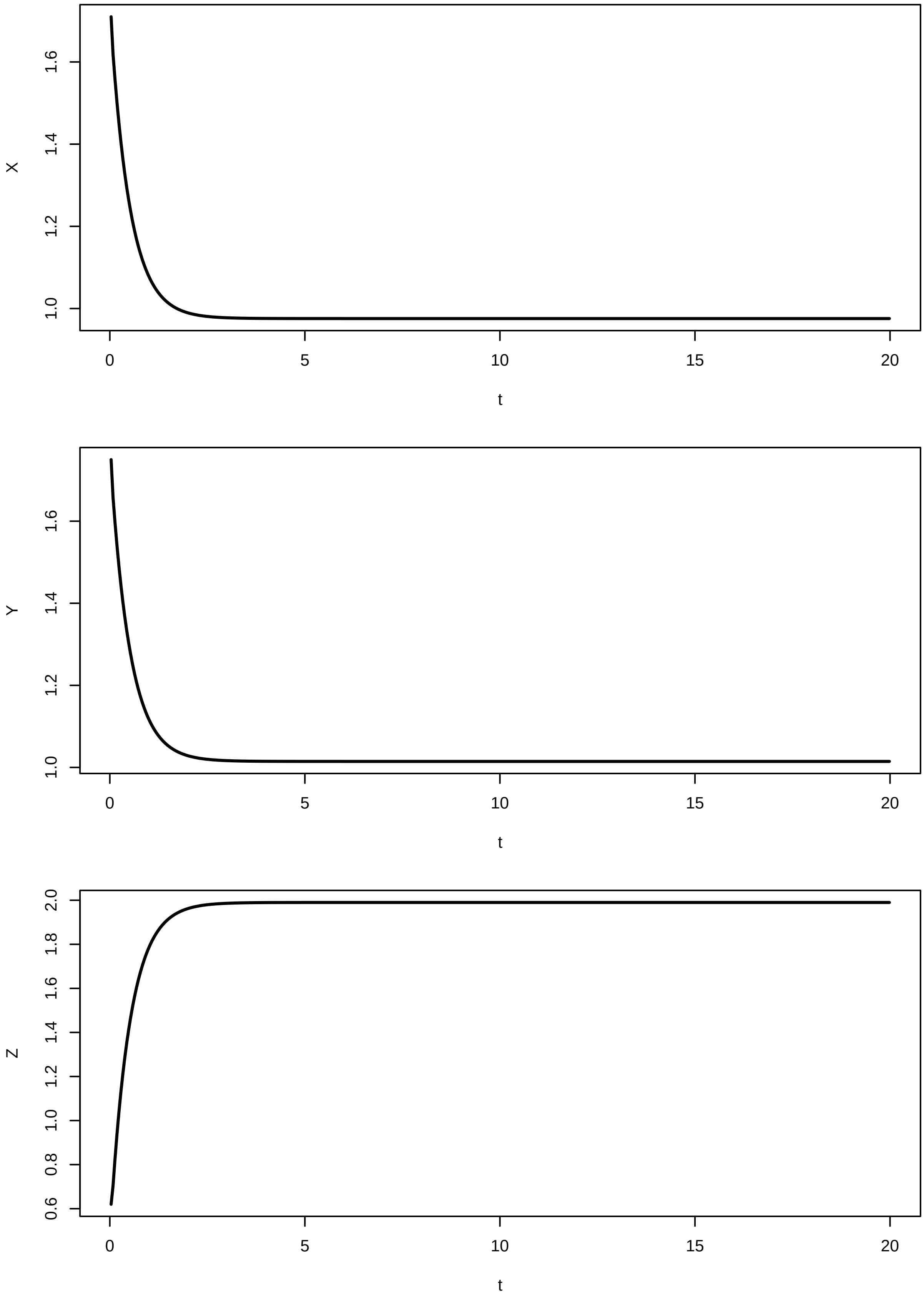
Each model contains only these initial conditions, the concentration values (x,y,z) and two extra parameters k_+ and k_-. The coefficients k_+ and k_- are rate parameters (not rates) with units of 1/micromolar*hours and 1/hours respectively. These parameters are unknown and can only be estimated using parameter fitting.

(b)

```r
# set initial values -
# these have been chosen as the first values available from experimental data (Table 2)
d11 = 1.71
d12 = 0.62
d22 = 1.75

# function containing diff equations of x,y,z
dimer_func <- function(t, state, parameters) {

  with(as.list(c(state, parameters)),{
    # rate of change
    dX <- k_p*(2*d11 + d12 - 2*X - Z)^2 - k_m*X   #X
    dY <- k_p*(2*d22 + d12 - 2*Y - Z)^2 - k_m*Y   #Y
    dZ <- 2*k_p*(2*d11 + d12 - 2*X - Z)*(2*d22 + d12 - 2*Y - Z)  - k_m*Z #Z

    # return the variables rate of change
    list(c(dX, dY, dZ))
  })
}

# declare variables & assign initial conditions
dimer <- c(X = d11, Y = d22, Z = d12)
# time sequence over which the model is deployed
times <- seq(1/30, 20, by = 0.05)
# declare parameters
parameters <- c(k_p = 200,k_m = 2)
# fit using lsode()
out <- lsode(y = dimer, times = times, func = dimer_func, parms = parameters)
# get summary of output
summary(out)
```

```
##                   X           Y           Z
## Min.      0.9756464   1.01466846   0.6200000
## 1st Qu.   0.9756464   1.01466846   1.9898662
## Median    0.9756464   1.01466846   1.9899323
## Mean      0.9943573   1.03338181   1.9527576
## 3rd Qu.   0.9756795   1.01470154   1.9899323
## Max.      1.7100000   1.75000000   1.9899323
## N       400.0000000 400.00000000 400.0000000
## sd        0.0818869   0.08190834   0.1616701
```

```r
# plot results i.e how X, Y and Z progress over time
# initialise plot frames
par( mar = c(4, 4, 2, 2.1), mfrow = c(3,1) )

# plot X over time
plot(out[, c("time")],out[, c("X")], type = "l", lwd = 2, xlab = "t", ylab = "X",)

# plot Y over time
plot(out[, c("time")],out[, c("Y")], type = "l", lwd = 2, xlab = "t", ylab = "Y",)

# plot Z over time
plot(out[, c("time")],out[, c("Z")], type = "l", lwd = 2, xlab = "t", ylab = "Z",)
```



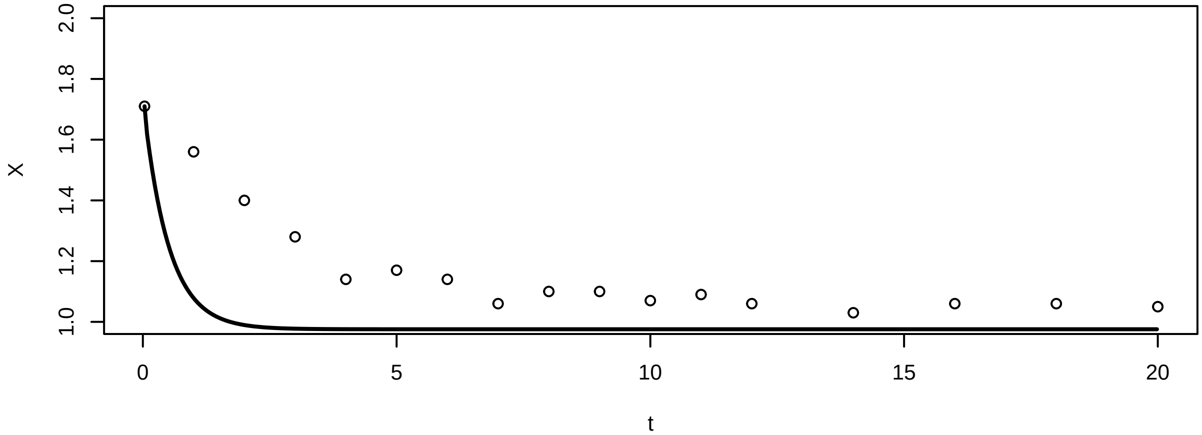
X
1.0
1.2
1.4
1.6
0
5
10
15
20
t
Y
1.0
1.2
1.4
1.6
0
5
10
15
20
t
Z
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0
5
10
15
20
t

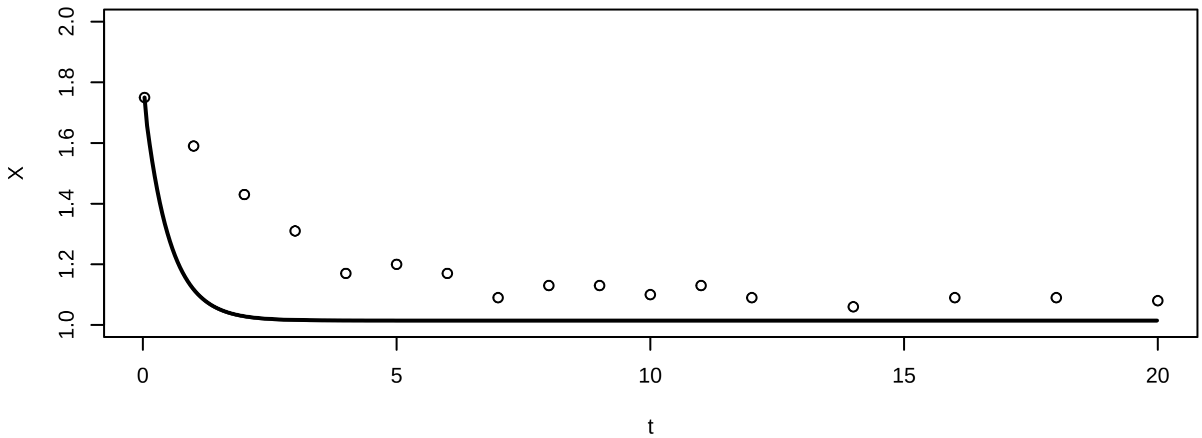
(c)

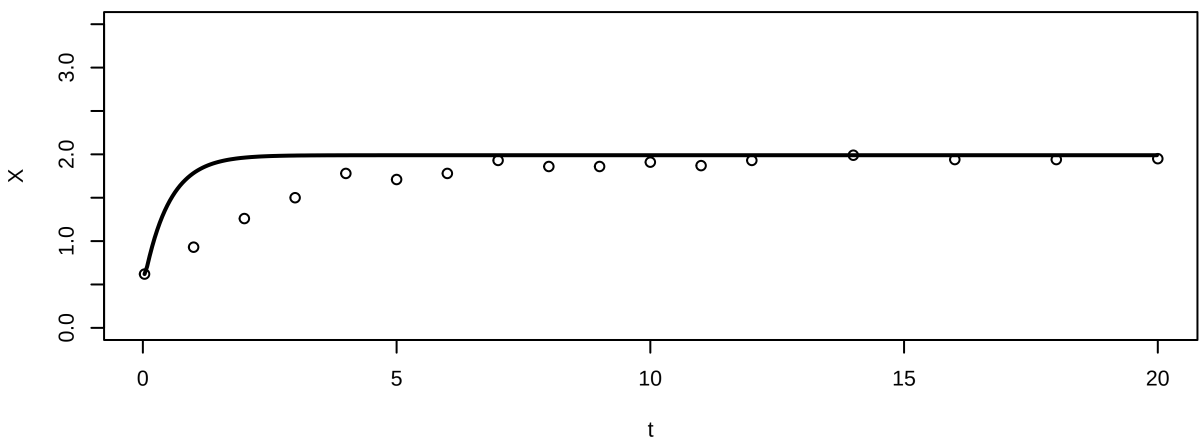
```r
# create dataframe of experimental data
time <- c(1/30 , 1 , 2 , 3 , 4 , 5 , 6 , 7 , 8 , 9 , 10 , 11 , 12 , 14 , 16 , 18 , 20)
D11 <- c(1.71 , 1.56 , 1.40 , 1.28 , 1.14 , 1.17 , 1.14 , 1.06 , 1.10 , 1.10 , 1.07 ,
         1.09 , 1.06 , 1.03 , 1.06 , 1.06 , 1.05)
D22 <- c(1.75 , 1.59 , 1.43 , 1.31 , 1.17 , 1.20 , 1.17 , 1.09 , 1.13 , 1.13 , 1.10 ,
         1.13 , 1.09 , 1.06 , 1.09 , 1.09 , 1.08)
D12 <- c(0.62 , 0.93 , 1.26 , 1.50 , 1.78 , 1.71 , 1.78 , 1.93 , 1.86 , 1.86 , 1.91 ,
         1.87 , 1.93 , 1.99 , 1.94 , 1.94 , 1.95)
table2_df <- data.frame(time,D11,D22, D12)
names(table2_df)=c("time","D11","D22", "D12")
table2_df
```

```
##          time  D11  D22  D12
## 1   0.03333333 1.71 1.75 0.62
## 2   1.00000000 1.56 1.59 0.93
## 3   2.00000000 1.40 1.43 1.26
## 4   3.00000000 1.28 1.31 1.50
## 5   4.00000000 1.14 1.17 1.78
## 6   5.00000000 1.17 1.20 1.71
## 7   6.00000000 1.14 1.17 1.78
## 8   7.00000000 1.06 1.09 1.93
## 9   8.00000000 1.10 1.13 1.86
## 10  9.00000000 1.10 1.13 1.86
## 11 10.00000000 1.07 1.10 1.91
## 12 11.00000000 1.09 1.13 1.87
## 13 12.00000000 1.06 1.09 1.93
## 14 14.00000000 1.03 1.06 1.99
## 15 16.00000000 1.06 1.09 1.94
## 16 18.00000000 1.06 1.09 1.94
## 17 20.00000000 1.05 1.08 1.95
```

```r
# overlay data on plots of solution from q2b
# initialise plot frames
par( mar = c(4, 4, 2, 2.1), mfrow = c(3,1) )

# plot X over time + experimental data points
plot(out[, c("time")] ,out[, c("X")], type = "l", lwd = 2, xlab = "t", ylab = "X",ylim=c(1,2))
points(table2_df$time, table2_df$D11)

# plot Y over time + experimental data points
plot(out[, c("time")] ,out[, c("Y")], type = "l", lwd = 2, xlab = "t", ylab = "X",ylim=c(1,2))
points(table2_df$time, table2_df$D22)

# plot Z over time + experimental data points
plot(out[, c("time")] ,out[, c("Z")], type = "l", lwd = 2, xlab = "t", ylab = "X",ylim=c(0,3.5))
points(table2_df$time, table2_df$D12)
```







It's clear the parameter values used ($k_+ = 200$,$k_- = 2$) does not create a model that adequately fit the experimental data. A Levenberg–Marquardt least-squares error algorithm is used to find the best fit k_+ and k_-.

```r
# function to minimize as part of levenberg marquart algorithm
ssq=function(pars){

  # variables & initial concentrations
  cinit=c(X = 1.71, Y = 1.75, Z = 0.62)
  # time sequence, expanded to expanded for better fit
  t=c(seq(0,5,0.05),table2_df$time)
  t=sort(unique(t))
  # get parameter values
  k_p1 = pars[1]
  k_m1 = pars[2]

  # fit model
  out=lsode(y=dimer , times=t , func=dimer_func , parms = list(k_p = k_p1, k_m = k_m1))

  # extract and format output to match time of experimental data
  outdf = data.frame(out)
  outdf=outdf[outdf$time %in% table2_df$time,]
  # extract X/Y/Z output
  xout = outdf$X ; yout = outdf$Y ; zout = outdf$Z
  # extract corresponding experimental results
  xdata = table2_df$D11 ; ydata = table2_df$D22 ; zdata = table2_df$D12
  # calculate squared difference
  ssqres = (xout-xdata)^2 + (yout-ydata)^2 + (zout-zdata)^2

  # return squared difference
  return(ssqres)
}

# parameter fitting using levenberg marquart algorithm
# initial guess for parameters
# NOTE: algorithm wouldn't work when i set the initial k_p = 200
parms <- c(k_p = 50,k_m = 2)

# fitting
fitval=nls.lm(par=parms,fn=ssq)
```

```r
# Summary of fit
summary(fitval)$coefficients
```

```
##        Estimate   Std. Error     t value     Pr(>|t|)
## k_p 347.4544192 3945.7883598  0.08805703 9.309962e-01
## k_m   0.3244745    0.0261858 12.39124047 2.784800e-09
```

Using the data in Table 2 to the solutions of equations (3.10a), (3.10b) and (3.10c), according to the Levenberg-Marquardt least-squares algorithm, the best fit estimates for k_+ and k_- were found to be 347.4544192 and 0.3244745 respectively.

```r
# Estimated parameter
parest=as.list(coef(fitval))
parest
```

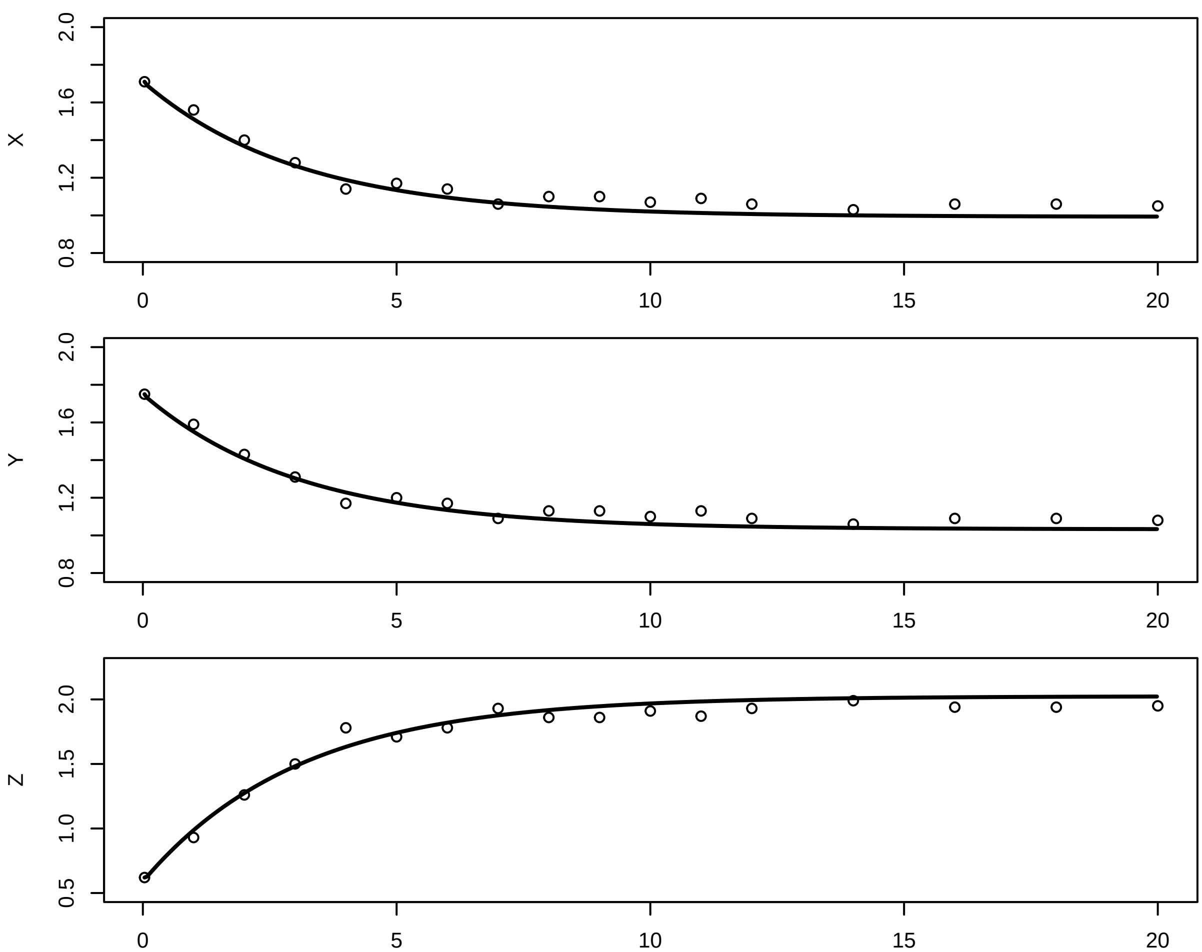
```
## $k_p
## [1] 347.4544
##
## $k_m
## [1] 0.3244745
```

(d)

The implementation of Levenberg-Marquardt least-squares algorithm (LMA) works by taking an initial estimate for the parameters, fitting a model using those, calculating the error of the output of the model, in this instance the squared difference of each variable to the experimental data is taken. LMA interpolates between the Gauss–Newton algorithm and the method of gradient descent which means that in many cases it finds a solution even if it starts very far off the final minimum. As with other iterative algorithms LMA finds only a local minimum which may not be the global minimum. Due to this any best fit parameters need to be assessed on how well the model using them fits the data.

A model is fitted with these best estimates and plotted along with the experimental data as was done before.

```r
# fit model as before but with best fit parameters
out2 = lsode(y=dimer,times=times,func=dimer_func,parms=list(k_p=parest$k_p, k_m=parest$k_m))
par( mar = c(2, 4, 1, 2.1), mfrow = c(3,1) )
# overlay data on plots of solution from out2 for x,y and z
plot(out2[, c("time")] ,out2[, c("X")], type = "l", lwd = 2, xlab = "t", ylab = "X",ylim=c(0.8,2))
points(table2_df$time, table2_df$D11)
plot(out2[, c("time")] ,out2[, c("Y")], type = "l", lwd = 2, xlab = "t", ylab = "Y",ylim=c(0.8,2))
points(table2_df$time, table2_df$D22)
plot(out2[, c("time")] ,out2[, c("Z")], type = "l", lwd = 2, xlab = "t", ylab = "Z",ylim=c(0.5,2.25))
points(table2_df$time, table2_df$D12)
```



These parameters provide a much better fit to the data than $k_+ = 200$,$k_- = 2$ and almost an exact fit to the data, passing at least partially though the many of all data point across the three variables. These are both increases on the best fit parameters corresponding to the same data in the article,best fit parameters of (k^+, k^-) were found to be 284 and 0.238 respectively. In general, the fit the model provides the experimental data slightly lessens as t increases, possibly indicating a sensitivity to the parameters that increases as time increases.

(e)

The various sensitivities for the variables x,y and z to the parameters k_+ and k_- are given as

$$S_{11} = \frac{\partial x}{\partial k_+} \;\; ; \;\; S_{21} = \frac{\partial y}{\partial k_+} \;\; ; \;\; S_{31} = \frac{\partial z}{\partial k_+}$$

$$S_{12} = \frac{\partial x}{\partial k_-} \;\; ; \;\; S_{22} = \frac{\partial y}{\partial k_-} \;\; ; \;\; S_{32} = \frac{\partial z}{\partial k_-}$$

The sensitivity equations were derived to be

$$\begin{aligned}\frac{\partial S_{11}}{\partial t} =& (2d_{11} + d_{12} - 2x - z)^2 \\ & - S_{11}(4K^+(2d_{11} + d_{12} - 2x - z) + K^-) \\ & - S_{31}(2K^+(2d_{11} + d_{12} - 2x - z))\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{12}}{\partial t} =& - S_{12}(4K^+(2d_{11} + d_{12} - 2x - z) + K^-) \\ & - S_{32}(2K^+(2d_{11} + d_{12} - 2x - z)) \\ & - x\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{21}}{\partial t} =& (2d_{22} + d_{12} - 2y - z)^2 \\ & - S_{21}(4K^+(2d_{22} + d_{12} - 2y - z) + K^-) \\ & - S_{31}(2K^+(2d_{22} + d_{12} - 2y - z))\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{22}}{\partial t} =& - S_{22}(4K^+(2d_{22} + d_{12} - 2y - z) + K^-) \\ & - S_{32}(2K^+(2d_{22} + d_{12} - 2y - z)) \\ & - y\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{31}}{\partial t} =& 2(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) \\ & - S_{11}4K^+(2d_{22} + d_{12} - 2y - z) \\ & - S_{21}4K^+(2d_{11} + d_{12} - 2x - z) \\ & - S_{31}(4K^+(d_{11} + d_{22} + d_{12} - x - y - z) + K^-)\end{aligned}$$

$$\begin{aligned}\frac{\partial S_{32}}{\partial t} =& - S_{12}4K^+(2d_{22} + d_{12} - 2y - z) \\ & - S_{22}4K^+(2d_{11} + d_{12} - 2x - z) \\ & - S_{32}(4K^+(d_{11} + d_{22} + d_{12} - x - y - z) + K^-) \\ & - z\end{aligned}$$

Solutions over next four pages

$$\frac{\partial x}{\partial t} = K^+(2d_{11} + d_{12} - 2x - z)^2 - K^- x$$

$$S_{11} = \frac{\partial x}{\partial K^+} \;;\; \frac{\partial S_{11}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial x}{\partial K^+}\right) = \frac{\partial}{\partial K^+}\left(\frac{\partial x}{\partial t}\right)$$

$$\frac{\partial S_{11}}{\partial t} = \frac{\partial}{\partial K^+}\left(K^+(2d_{11} + d_{12} - 2x - z)^2 - K^- x \right)$$

$$= (2d_{11} + d_{12} - 2x - z)^2 + K^+(2)(2d_{11} + d_{12} - 2x - z)\left(-2\frac{\partial x}{\partial K^+} - \frac{\partial z}{\partial K^+}\right)$$
$$- K^- \frac{\partial x}{\partial K^+}$$

$$= (2d_{11} + d_{12} - 2x - z)^2 - 4K^+(2d_{11} + d_{12} - 2x - z)S_{11}$$
$$- 2K^+(2d_{11} + d_{12} - 2x - z)S_{31} - K^- S_{11}$$

$$= (2d_{11} + d_{12} - 2x - z)^2 - S_{11}\left(4K^+(2d_{11} + d_{12} - 2x - z) - K^-\right)$$
$$- S_{31}(2K^+)(2d_{11} + d_{12} - 2x - z)$$

$$S_{12} = \frac{\partial x}{\partial K^-} \;;\; \frac{\partial S_{12}}{\partial t} = \frac{\partial}{\partial t}\frac{\partial x}{\partial K^-} = \frac{\partial}{\partial K^-}\left(\frac{\partial x}{\partial t}\right)$$

$$\frac{\partial S_{12}}{\partial t} = \frac{\partial}{K^-}\left(K^+(2d_{11} + d_{12} - 2x - z)^2 - K^- x \right)$$

$$= K^+(2)(2d_{11} + d_{12} - 2x - z)\left(-2\frac{\partial x}{\partial K^-} - \frac{\partial z}{\partial K^-}\right) - K^-\frac{\partial x}{\partial K^-} - x$$

$$= -4S_{12}K^+(2d_{11} + d_{12} - 2x - z) - 2S_{32}K^+(2d_{11} + d_{12} - 2x - z)$$
$$- S_{12}K^- - x$$

$$= S_{12}\left(-4K^+(2d_{11} + d_{12} - 2x - z) - K^-\right)$$
$$+ S_{32}\left(-2K^+(2d_{11} + d_{12} - 2x - z) - x\right.$$

∂t

$$S_{21} = \frac{\partial y}{\partial K^+} \quad ; \quad \frac{\partial S_{21}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial y}{\partial K^+}\right) = \frac{\partial}{\partial K^+}\left(\frac{\partial y}{\partial t}\right)$$

$$\frac{\partial S_{21}}{\partial t} = \frac{\partial}{\partial K^+}\left(K^+(2d_{22}+d_{12}-2y-z)^2 - K^- y \right)$$

$$= (2d_{22}+d_{12}-2y-z)^2 + K^+(2)(2d_{22}+d_{12}-2y-z)\left(-2\frac{\partial y}{\partial K^+} - \frac{\partial z}{\partial K^+}\right)$$
$$- K^- \frac{\partial y}{\partial K^+}$$

$$= (2d_{22}+d_{12}-2y-z)^2 - 4K^+S_{21}(2d_{22}+d_{12}-2y-z) \cancel{-2K^+(}$$
$$- 2K^+(2d_{22}+d_{12}-2y-z)S_{31} - K^- S_{21}$$
$$= (2d_{22}+d_{12}-2y-z)^2 + S_{21}\left(-4K^+(2d_{22}+d_{12}-2y-z) - K^-\right)$$
$$\cancel{-2K^+} + S_{31}\left(-2K^+(2d_{22}+d_{12}-2y-z)\right)$$

$$S_{22} = \frac{\partial y}{\partial K^-} \quad ; \quad \frac{\partial S_{22}}{\partial t} = \frac{\partial}{\partial t}\frac{\partial y}{\partial K^-} = \frac{\partial}{\partial K^-}\left(\frac{\partial y}{\partial t}\right)$$

$$\frac{\partial S_{22}}{\partial t} = \frac{\partial}{\partial K^-}\left(K^+(2d_{22}+d_{12}-2y-z)^2 - K^- y \right)$$

$$= K^+(2)(2d_{22}+d_{12}-2y-z)\left(-2\frac{\partial y}{\partial K^-} - \frac{\partial z}{\partial K^-}\right)$$
$$- y - K^- \frac{\partial y}{\partial K^-}$$
$$= -4K^+ S_{22}(2d_{22}+d_{12}-2y-z) - 2K^+ S_{32}(2d_{22}+d_{12}-2y-z)$$
$$- y - S_{22} K^{-1}$$
$$= S_{22}\left(-4K^+(2d_{22}+d_{12}-2y-z) - K^-\right)$$
$$+ \cancel{2K^+} S_{32}\left(-2K^+(2d_{22}+d_{12}-2y-z)\right) - y$$

$$\frac{\partial z}{\partial t} = 2K^+(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) - K^- z$$

$$S_{31} = \frac{\partial z}{\partial K^+} \; ; \; \frac{\partial S_{31}}{\partial t} = \frac{\partial}{\partial t}\frac{\partial z}{\partial K^+} = \frac{\partial}{\partial K^+}\left(\frac{\partial z}{\partial t}\right)$$

$$\begin{aligned}
\frac{\partial S_{31}}{\partial t} &= \frac{\partial}{\partial K^+}\Big(2K^+(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) - K^- z\Big) \\
&= 2(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) \\
&\quad + 2K^+\left(2d - 2\frac{\partial x}{\partial K^+} - \frac{\partial z}{\partial K^+}\right)(2d_{22} + d_{12} - 2y - z) \\
&\quad + 2K^+(2d_{11} + d_{12} - 2x - z)\left(-2\frac{\partial y}{\partial K^+} - \frac{\partial z}{\partial K^+}\right) \\
&\quad - K^- \frac{\partial z}{\partial K^+} \\
&= 2(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) \\
&\quad - 4K^+ S_{11}(2d_{22} + d_{12} - 2y - z) \\
&\quad - 2K^+ S_{31}(2d_{22} + d_{12} - 2y - z) \\
&\quad - 4K^+ S_{21}(2d_{11} + d_{12} - 2x - z) \\
&\quad - 2K^+ S_{31}(2d_{11} + d_{12} - 2x - z) \\
&\quad - K^- S_{31} \\
&= 2(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) \\
&\quad - 4K^+ S_{11}(2d_{22} + d_{12} - 2y - z) \\
&\quad - 4K^+ S_{21}(2d_{11} + d_{12} - 2x - z) \\
&\quad - 2K^+ S_{31}(2d_{11} + 2d_{12} + 2d_{22} - 2y - 2x - 2z) \\
&\quad - K^- S_{31} \\
&= 2(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) \\
&\quad - S_{11} 4K^+(2d_{22} + d_{12} - 2y - z) \\
&\quad - S_{21} 4K^+(2d_{11} + d_{12} - 2x - z) \\
&\quad - S_{31}\big(4K^+(d_{11} + d_{12} + d_{22} - y - x - z) + K^-\big)
\end{aligned}$$

$$\frac{\partial z}{\partial t} = 2K^+(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) - K^- z$$

$$S_{32} = \frac{\partial z}{\partial K^-} \quad ; \quad \frac{\partial S_{32}}{\partial t} = \frac{\partial}{\partial t}\left(\frac{\partial z}{K^-}\right) = \frac{\partial}{\partial K^-}\left(\frac{\partial z}{\partial t}\right)$$

$$\frac{\partial S_{32}}{\partial t} = \frac{\partial}{\partial K^-}\Big(2K^+(2d_{11} + d_{12} - 2x - z)(2d_{22} + d_{12} - 2y - z) - K^- z\Big)$$

$$= 2K^+(2d_{11} + d_{12} - 2x - z)\left(-2\frac{\partial y}{\partial K^-} - \frac{\partial z}{\partial K^-}\right)$$
$$+ 2K^+\left(0 - 2\frac{\partial x}{\partial K^-} - \frac{\partial z}{\partial K^-}\right)(2d_{22} + d_{12} - 2y - z)$$
$$- z - K^- \frac{\partial z}{\partial K^-}$$

$$= -4K^+ S_{22}(2d_{11} + d_{12} - 2x - z) - 2K^+ S_{32}(2d_{11} + d_{12} - 2x - z)$$
$$-4K^+ S_{12}(2d_{22} + d_{12} - 2y - z) - 2K^+ S_{32}(2d_{22} + d_{12} - 2y - z)$$
$$- z - S_{32} K^-$$

$$= -S_{12}(4K^+(2d_{22} + d_{12} - 2y - z))$$
$$- S_{22}(4K^+(2d_{11} + d_{12} - 2x - z))$$
$$- S_{32}(2K^+(2d_{11} + 2d_{22} + 2d_{12} - 2x - 2y - z) + K^-)$$
$$- z$$

$$= -S_{12}(4K^+(2d_{22} + d_{12} - 2y - z))$$
$$- S_{22}(4K^+(2d_{11} + d_{12} - 2x - z))$$
$$- S_{32}(4K^+(d_{11} + d_{22} + d_{12} - x - y - z) + K^-)$$
$$- z$$

The the difference between sensitivities derived here and the sensitivities in the article is the absence, in the article derived equations, of the terms of the sensitivity of the other variables not used in the sensitivity equations e.g. in the article sensitivity equation of x with respect to k^+ (S_{11}), it does not contain the term involving the sensitivity of z with respect to k^+ (S_{31}). Similar absences are repeated across all six sensitivity equations.

In the article, data from Table 2 leads to best fit parameters (k^+ , k^-) to be 284 and 0.238 respectively. These are both a decrease of 28% and 24% from the best-fit parameters you obtained from my analysis of the data, 347.4544192 and 0.3244745 respectively.

For the purposes of this question, the differences between the sensitivities derived here and the sensitivities in the article are isolated below

$$(diff)\frac{\partial S_{11}}{\partial t} = -S_{31}(2K^+(2d_{11} + d_{12} - 2x - z))$$

$$(diff)\frac{\partial S_{12}}{\partial t} = -S_{32}(2K^+(2d_{11} + d_{12} - 2x - z))$$
$$(diff)\frac{\partial S_{21}}{\partial t} = -S_{31}(2K^+(2d_{22} + d_{12} - 2y - z))$$
$$(diff)\frac{\partial S_{22}}{\partial t} = -S_{32}(2K^+(2d_{22} + d_{12} - 2y - z))$$

$$\begin{aligned}(diff)\frac{\partial S_{31}}{\partial t} = &- S_{11}4K^+(2d_{22} + d_{12} - 2y - z)\\ &- S_{21}4K^+(2d_{11} + d_{12} - 2x - z)\end{aligned}$$

$$\begin{aligned}(diff)\frac{\partial S_{32}}{\partial t} = &- S_{12}4K^+(2d_{22} + d_{12} - 2y - z)\\ &- S_{22}4K^+(2d_{11} + d_{12} - 2x - z)\end{aligned}$$

All six equations above are very similar in structure, they all contain a minus sensitivity term (e.g. -S_{11} etc.), a k^+ term, factored either by 2 or 4 and a term which is the difference between two of the variables and their initial values e.g. $2d_{22} + d_{12} - 2y - z$. Observing the progression of the models and the data, x and y are constantly decreasing and z is constantly increasing i.e. $x < d_{11}$, $y < d_{12}$ and $z > d_{12}$. This overall term will largely be positive as the difference between the d_{11}/d_{22} and x/y is doubled and should be greater than the difference between d_{12} and z. In both sets of parameters, k^+ and k^- are both positive, by definition they are rate parameters and will be always be greater than zero. In effect, these terms only act as a scale for the minus sensitivity in the $diff$ equations. If the sensitivity in the $diff$ equation is positive then the overall $diff$ equation will be negative and vice-versa.

Once again, the diff equations are the difference in the sensitivity equations for the variables x,y,z and the parameters k^+ and k^- between my derivations and the derivations in the article. As **(1)** all the $diff$ equations are of similar structure and are interconnected i.e. a sensitivity equation of x is affected by a sensitivity of z but the same sensitivity equation of z is affected by the sensitivity of x and **(2)**, as shown above, the $diff$ equations have an opposite effect i.e. it will be a negatively scaled value of the sensitivity, then the overall effect of these terms will reduce the sensitivity of our variables to the parameters.

As the sensitivity equations quoted in the article lack these elements absent, there is an increased sensitivity to the parameters so any best-fit estimate of their values will be reduced to compensate for this extra sensitivity. This is why the best-fit parameters from the article are less than the the best-fit parameters derived in the assignment above.