Comparing Two Different Models.

The comparison of two different models of the Central Regulatory Circuit of Drosophila.

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Abstract

Mechanoreceptors, are located in a well-organized and controlled way on the *Drosophila melanogaster* head and body, whose genetic support is described in terms of gene networks. Structure of position of 26 macrochaete on the surface of fly head and body, the so-called bristle pattern. [1]

In this work, we established and observed two different models of Central Regulatory Circuit of Drosophila (CRC) from different articles and compared them. The models describe the Central Regulatory Circuit which acts in the early stage of the *Drosophila melanogaster* mechanoreceptors morphogenesis. The main component of the Central Regulatory Circuit is the complex of *Achaete-Scute* genes.

Abbreviations

CRC : Central Regulatory Circuit

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Introduction

The large bristles function as mechanoreceptors appear for elements of the peripheral nervous system in the drosophila body. This bristles structure is practically unchanged in all the species representatives and is a taxonomic character. A mechanoreceptor is made up out of four cells: shaft (trichogen), socket (tormogen), neuron, and glial cell (thecogen). The parent of all these components is the single parental cell (SOP cell—Sensory Organ Precursor cell). [2]

Formalized description, systematization, and analysis of gene networks with the help of mathematical and numerical modeling allow to understand mechanisms of functioning of these systems and to predict their behavior in different conditions. On the other hand, this mathematical approach gives possibility to construct artificial analogues of these natural systems in order to use them in various applications.

Goal

The main aim of our work is elaboration of mathematical tools which allow giving full description of the CRC circuit. With the help of 2 different articles with different models.

Theory

Morphogenesis of drosophila mechanoreceptor is a perfect example of a gene network supporting acyclic processes. Which ensures reaching a steady finite state.

Two different models have been searched for. Both models deal with the CRC circuit, but they use different models.

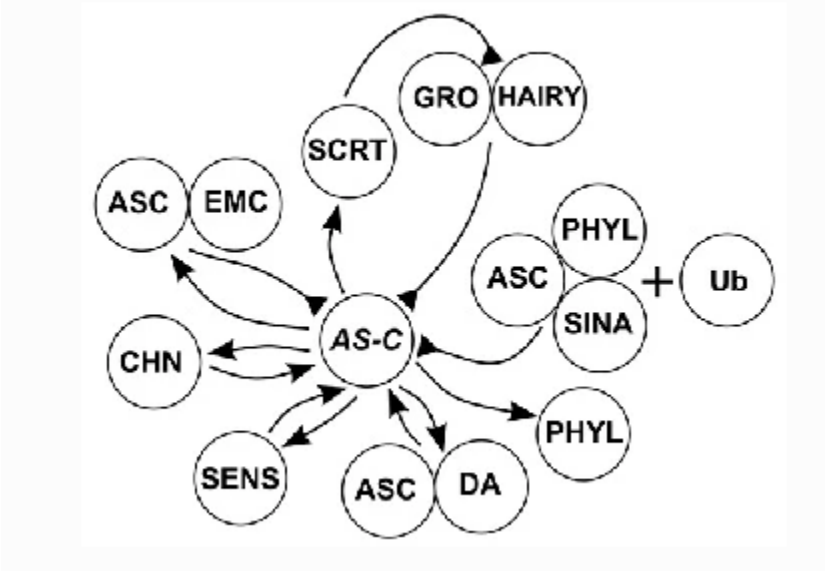

Figure 1: The CRC of the gene networks of the morphogenesis system of Drosophila mechanoreceptors.

This is the first model [3].

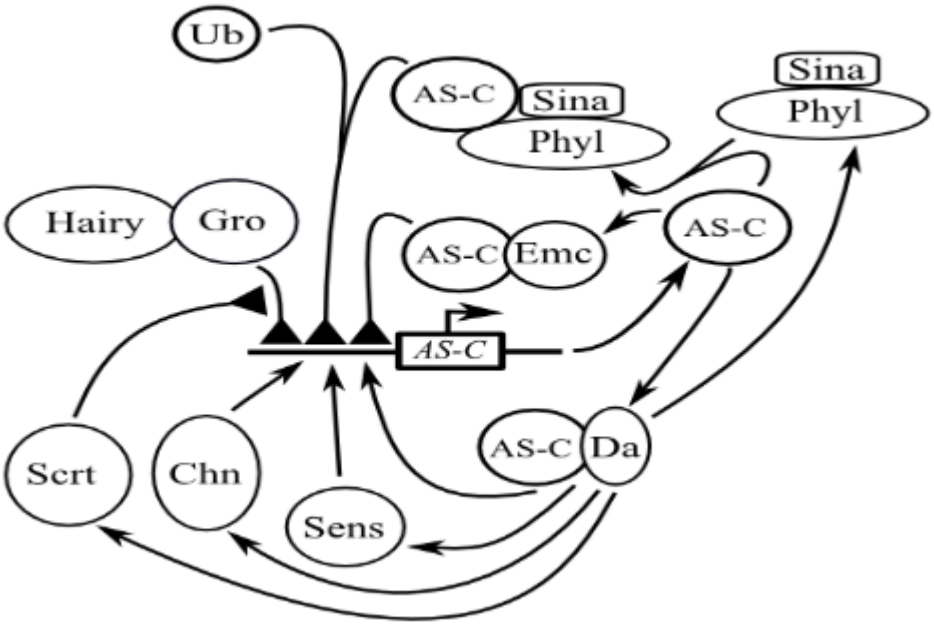

Figure 2: The other CRC of the gene networks of the morphogenesis system of Drosophila mechanoreceptors.

This is the other model that has been created by the second article [4].

From both models, 6 proteins were extracted. Since these are the most important or have the most influence. These 6 proteins are: Acaete-Scute (AS-C), Hairy, Senseless (SENS), Scratch (SCRT), Charlatan (CHN), Phyllopod (PHYL). These are shown in the graphs

Daughterless (DA), Extramacrochaete (EMC), Groucho (GRO), Seven in one (SINA) and Ubiquitin (UB) are also important proteins, but the content of these is almost unchanged, shown by study [3].

Methods

Since we have 2 models, we also have 2 equations.

This is the differential equation of the first article [1]:

$\frac{dx}{dt} = k_x \frac{\sigma_1(Dx)+\sigma_3(z)+\sigma_5(w)}{(1+Gy)(1+Ex)} - (1 + p(t - \Delta t)US)m_x x$
$\frac{dy}{dt} = k_y \frac{C}{d1+u^{m_r}}$
$\frac{dz}{dt} = k_z s_3(Dx) - m_s z$
$\frac{du}{dt} = k_u s_4(Dx) - m_u u$
$\frac{dw}{dt} = k_w s_5(Dx) - m_w w$
$\frac{dp}{dt} = k_p \frac{s_6(Dx)h(t-\Delta t)(t-\Delta t^2)}{L+h(t-\Delta t)(t-\Delta t)^2}$

In the last equation we use a Heaviside function, *h(t)*, that express the decomposition of the process with some delay of $t = 12$.

This is the other model that has been created by the second article [2]. This is the differential equation used by the article:

$\frac{dx}{dt} = \frac{\sigma_1(Dx)+\sigma_3(z)+\sigma_5(w)}{(1+Gy)(1+Ex)} - k_x(1 + p(t - \Delta t)US)x$
$\frac{dy}{dt} = \frac{C}{d1+u} - k_y y$
$\frac{dz}{dt} = s_3(Dx) - k_z z$
$\frac{du}{dt} = s_4(Dx) - k_u u$
$\frac{dw}{dt} = s_5(Dx) - k_w w$
$\frac{dp}{dt} = \frac{s_6(Dx)h(t-\Delta t)(t-\Delta t^2)}{1+(t-\Delta t)^2} - k_p p$

Here are all the params and state values.

dt_x = dt_y = dt_z = dt_u = dt_w = dt_p = u0 = w0 = p0 -> 0, *Gro = EMC = C = m1 = m2 = m3 = m4 = m5 = m6 = m7 = L = kx = ky = kz = ku = kw = kp -> 1*, *D -> 2.05*, *UB -> 1.17*, *SINA -> 5.6*, *n1 = n3 = n5 -> 2*, *a3 -> 3.61*, *b3 -> 4.96*, *c3 -> 1.35*, *a4 -> 4.43*, *b4 -> 6.09*, *c4 -> 1.66*, *a5 -> 8.09*, *b5 -> 11.13*, *c5 -> 3.03*, *a6 -> 2.67*, *b6 -> 3.67*, *c6 -> 1.00*, *d1 -> 7.46*, *d3 -> 2.77*, *d5 -> 1.24*, *y0 -> 3* and *x0 = z0 -> 3 / 20*

The sigma function σ functions l = 1,3,5 and $s_i > 0, i = 3, 4, 5, 6$ are positive and describe the positive feedback.

Result

The result of this research papers are two graphs showing the models and the difference.

Models

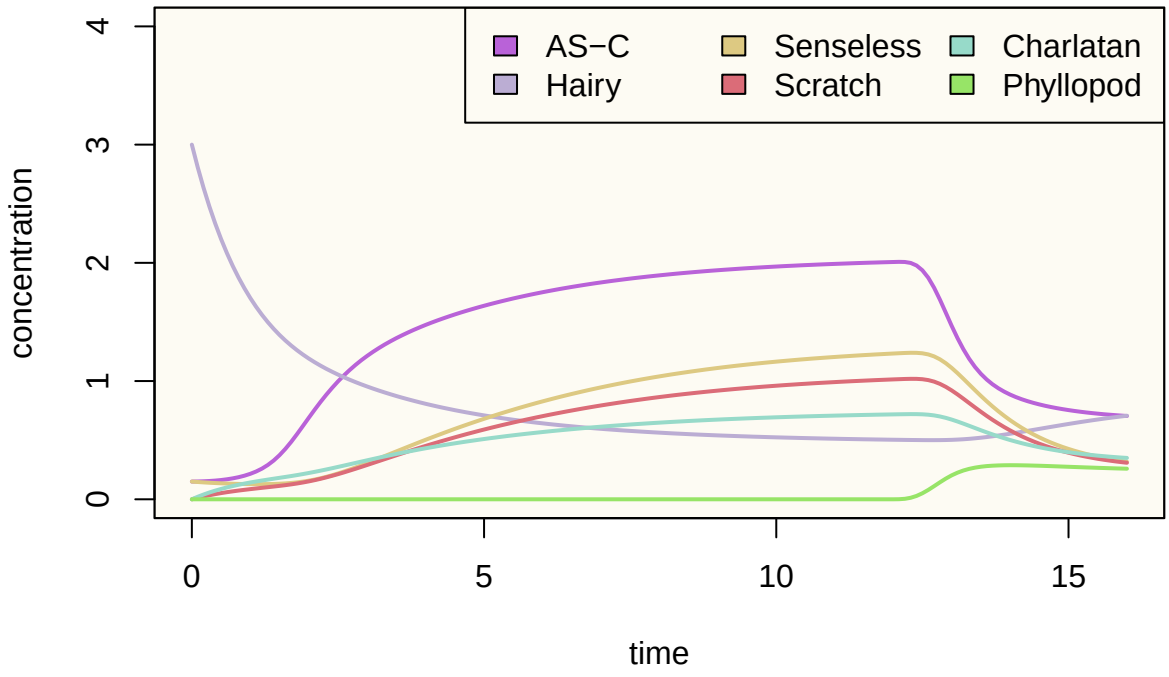

Figure 3: The CRC model of the first article

The *AS-C* curve increases immediately and reached a steady state, after a while it decreases to about a concentration of below 1. The curve of *Hairy* goes steadily down until *AS-C* decreases. Then the concentration went up.

The other curves *Senseless*, *Scratch* and *Charlatan* all followed the same curve just with a lower value, and it steady went down at the same time point as *AS-C*.

Phyllopod stays the whole time around 0, until all the others one decreases/increases.

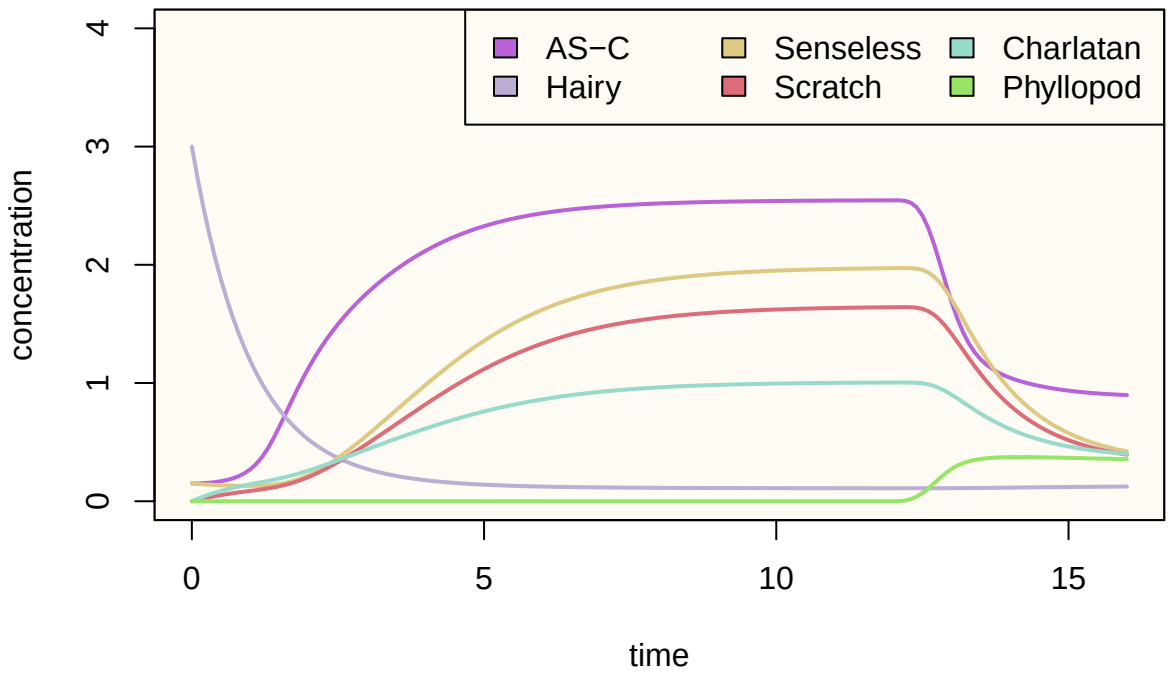

Figure 4: The CRC model of the second article

The curve of *Hairy* goes steadily down until it reached a steady state. *AS-C* curve reaches a steady state pretty quick, after a while it nose dives to about a concentration of 1.

At the same time, other curves *Senseless*, *Scratch* and *Charlatan* all followed the same curve just with a lower value, and it steady went down at the same time point as *AS-C*.

Phyllopod stays the whole time around 0, until all the others one, except *hairy*, reduce.

Discussion

We have encountered problems in this paper. There is no concrete experimental data. There is a site, FlyAtlas, but you cannot actually use it. Firstly, there is nothing about *AS-C*. And secondly, it is not clear which data we should use.

In the second article, they give other parameter values, but if you go to the site mentioned in the article. You get a graph with the same values as the first article, so we used these values. And we have not played with the parameters values to see what happens. But the first article did changed the values and their outcome was this: 'From the biological point of view, this means a ban on the formation of a mechanoreceptor' [3].

We now have two graphs, but we still do not really know which model uses the best differential equation.

Conclusion

Our goal was to compare two different models of the CRC of Drosophila. The conclusion we draw is that we compared the different models. But we lack the experimental data to see which is good.

We now have two graphs with two different CRC models, but as mentioned earlier, there is simply no/little experimental data. When more data emerges, we can really compare which model is the best. Or how we can then adjust it so that the model becomes even better.

References

[1] = Dagmara P. Furman, Tatyana A. Bukharina, (2019) 'The gene network determining development of Drosophila melanogaster mechanoreceptors' *sciencedirect* https://www.sciencedirect.com/science/article/abs/pii/S1476927109000292?via%3Dihub **24-05-22**
[2] = Vladimir P. Golubyatnikov, Tatyana A. Bukharina, Dagmara P. Furman, (2015) 'A model study of the morphogenesis of D. melanogaster mechanoreceptors: The central regulatory circuit' *worldscientific* https://www.worldscientific.com/doi/abs/10.1142/S0219720015400065 **24-05-22**
[3] = Bukharina, T.A., Akinshin, A.A., Golubyatnikov, V.P., (2020) 'Mathematical and Numerical Models of the Central Regulatory Circuit of the Morphogenesis System of Drosophila' *Springer* https://link.springer.com/article/10.1134/S1990478920020040 **24-05-22**
[4] = Ayupova, N.B., Demidenko, G.V., Matveeva, I.I., Fadeev, S.I, Zhubr , A.V. (2018) 'MATHEMATICAL AND NUMERICAL MODELS OF TWO ASYMMETRIC GENE NETWORKS' *nsc* http://semr.math.nsc.ru/v15/p1271-1283.pdf **24-05-22**

Appendix

```
# A function to plot the data
plotModel <- function(df){
plot(df$time, df$ASC, type='l',ylim=c(0, 4), col=cols[1], lwd=2, xlab="time",
     ylab="concentration")
lines(df$time, df$Hairy, col=cols[2], lwd=2)
lines(df$time, df$Senseless, col=cols[3], lwd=2)
lines(df$time, df$Scratch, col=cols[4], lwd=2)
lines(df$time, df$Charlatan, col=cols[5], lwd=2)
lines(df$time, df$Phyllopod, col=cols[6], lwd=2)
legend("topright",ncol=3, c("AS-C","Hairy","Senseless", "Scratch", "Charlatan",
                            "Phyllopod"), fill=c(cols[1],cols[2],cols[3],
                                                 cols[4], cols[5], cols[6]))
}

'%=%' <- function(x, y) {
  x <- as.character(substitute(x)[-1])
  if (length(y) < length(x))
    y <- rep(y, ceiling(length(x) / length(y)))
  if (length(y) > length(x))
    y <- y[1:length(x)]
  mapply(assign, x, y, MoreArgs = list(envir = parent.frame()))
  invisible()
}

# The Heaviside function
h <- function(i) i > 0

# The sigman functions
sigma1 <- function (v) {
  h(v) * d1 * v ^ n1 / (1 + v ^ n1)
}
sigma3 <- function (v) {
  h(v) * d3 * v ^ n3 / (1 + v ^ n3)
}
sigma5 <- function (v) {
  h(v) * d5 * v ^ n5 / (1 + v ^ n5)
}
s3 <- function (v) {
  h(v) * a3 * exp((v - b3) / c3) / (1 + exp((v - b3) / c3))
}
s4 <- function (v) {
  h(v) * a4 * exp((v - b4) / c4) / (1 + exp((v - b4) / c4))
}
s5 <- function (v) {
  h(v) * a5 * exp((v - b5) / c5) / (1 + exp((v - b5) / c5))
}
s6 <- function (v) {
  h(v) * a6 * exp((v - b6) / c6) / (1 + exp((v - b6) / c6))
}

# All the params
```

```
dt_x = 0
dt_y = 0
dt_z = 0
dt_u = 0
dt_w = 0
dt_p = 0
Gro = 1
EMC = 1
D = 2.05
UB = 1.17
SINA = 5.6
C = 1
n1 = 2
n3 = 2
n5 = 2
m1 = 1
m2 = 1
m3 = 1
m4 = 1
m5 = 1
m6 = 1
m7 = 1
L = 1
kx = 1
ky =1
kz = 1
ku = 1
kw = 1
kp = 1
a3 =  3.61
b3 = 4.96
c3 = 1.35
a4 = 4.43
b4 = 6.09
c4 = 1.66
a5 = 8.09
b5 = 11.13
c5 = 3.03
a6 = 2.67
b6 = 3.67
c6 = 1.00
d1 = 7.46
d3 = 2.77
d5 = 1.24
y0 = 3
x0 = 3 / 20
z0 = 3 / 20
u0 = 0
w0 = 0
p0 = 0

# The model of the first article
x_model <- function(t, dt, startValue, point, args, ...) {
```

```
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- kx * (sigma1(D * x) + sigma3(z) + sigma5(w)) / ((1 + Gro * y)
                                    * (1 + EMC * x)) - m1 * x
                                    * (1 + p_curr * UB * SINA)
  }
}
y_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- ky * C / (1 + u ^ m7) - m2 * y_curr
  }
}
z_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- kz * s3(D * x) - m3 * z_curr
  }
}
u_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- ku * s4(D * x) - m4 * u_curr
  }
}
w_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- kw * s5(D * x) - m5 * w_curr
  }
}
p_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- (s6(D * x) * h(t - 12) * (t - 12) ^ 2) /
                (1 + (t - 12) ^ 2) - kp * p_curr
  }
}

CRC.model <- function(t, p, parms, ...) {
       list(c(x_model(t, dt_x, x0, p), y_model(t, dt_y, y0, p),
```

```
              z_model(t, dt_z, z0, p), u_model(t, dt_u, u0, p),
              w_model(t, dt_w, w0, p), p_model(t, dt_p, p0, p)))
}

# Run the simulation
t <- seq(0, 16, by = 0.1)
start <- c(x0 * kx, y0 * ky, z0 * kz, u0 * ku, w0 * kw, p0 * kp)
traj <- data.frame(dede(start, t, func = CRC.model, parms = parameters))
cols <- distinctColorPalette(6)
plot.new()
rect(par("usr")[1], par("usr")[3],
     par("usr")[2], par("usr")[4],
     col = "#fdfbf3")
par(new = TRUE)
names(traj) <- c("time", "ASC", "Hairy", "Senseless",
                 "Scratch", "Charlatan", "Phyllopod")
plotModel(traj)

# The model of the second function
x_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- (sigma1(D * x) + sigma3(z) + sigma5(w)) /
      ((1 + Gro * y) * (1 + EMC * x)) - kx * (1 + p_curr * UB * SINA) * x
  }
}
y_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- (C / (d1 + u_curr)) - ky * y_curr
  }
}
z_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- s3(D * x) - kz * z_curr
  }
}
u_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- s4(D * x) - ku * u_curr
  }
}
w_model <- function(t, dt, startValue, point, args, ...) {
```

```
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- s5(D * x) - kw * w_curr
  }
}
p_model <- function(t, dt, startValue, point, args, ...) {
  if (t < 0) { startValue }
  else {
    c(x, y, z, u, w, p) %=% point
    c(x_curr, y_curr, z_curr, u_curr, w_curr, p_curr) %=% point
    lagPoint <- (s6(D * x) * h(t - 12) * (t - 12) ^ 2) /
      (1 + (t - 12) ^ 2) - kp * p_curr
  }
}

# Run it for the second article

traj.2 <- data.frame(dede(start, t, func = CRC.model, parms = parameters))
plot.new()
rect(par("usr")[1], par("usr")[3],
     par("usr")[2], par("usr")[4],
     col = "#fdfbf3")
par(new = TRUE)
names(traj.2) <- c("time", "ASC", "Hairy", "Senseless",
                   "Scratch", "Charlatan", "Phyllopod")
plotModel(traj.2)
```