Hodgkin-Huxley Piecewise Deterministic Markov Process

Hodgkin-Huxley Context

The Hodgkin-Huxley piecewise deterministic markov process is a model introduced by Alan Hodgkin and Andrew Huxley in 1952 with the paper “A quantitative description of membrane current and its application to conduction and excitation in nerve (https://pubmed.ncbi.nlm.nih.gov/12991237/).” The Hodgkin-Huxley model targets the initiation and propagation of an action potential in a neuron (e.g. current carried through a neuron with ions penetrating or charging its membrane).

As such, the capacitive current or capacitance flowing through the neuron’s membrane is defined as:

$$
\begin{aligned}
I &= C_m \frac{dV}{dt} + I_{ion} \\
C_m \frac{dV}{dt} &= -I_{ion} \\
I_{ion} &= g_{Na} m^3 h (V - E_{Na}) + g_K n^4 (V - E_K) + g_L (V - E_L)
\end{aligned}
$$

Where:

- I is current per unit area
- C_m is the capacitance (constant)
- V is the membrane voltage/potential
- I_{ion} is the current source caused by the Sodium (Na), Potassium (K) and other leaking (L) ions
- g_i is the electrical conductance of voltage-gated i-ion channels of the gates m, n, and h
- E is the equilibrium potential (voltage sources) of the gates associated with Sodium (Na), Potassium (K) and other leaking (L) ions

The Hodgkin-Huxley equation above is complemented with the following three differential equations:

$$
\begin{aligned}
\frac{dm}{dt} &= \alpha_m(V)(1 - m) - \beta_m(V) m \\
\frac{dh}{dt} &= \alpha_h(V)(1 - h) - \beta_h(V) h \\
\frac{dn}{dt} &= \alpha_n(V)(1 - n) - \beta_n(V) n
\end{aligned}
$$

The rate constants $\forall i \in \{Na, K, L\}$, α_i and β_i are rate functions estimated by fitting empirical functions of votage to the experimental data in the Hodgkin-Huxley paper such that:

$$
\begin{aligned}
\alpha_n &= 0{\cdot}01\ (V + 10) \Big/ \left(\exp \frac{V + 10}{10} - 1 \right), \\
\beta_n &= 0{\cdot}125 \exp\ (V/80), \\
\alpha_m &= 0{\cdot}1\ (V + 25) \Big/ \left(\exp \frac{V + 25}{10} - 1 \right), \\
\beta_m &= 4 \exp\ (V/18), \\
\alpha_h &= 0{\cdot}07 \exp\ (V/20), \\
\beta_h &= 1 \Big/ \left(\exp \frac{V + 30}{10} + 1 \right).
\end{aligned}
$$

In the original model, Hodgkin and Huxley established that there were three identical activation gates m and one gate h to explain the Sodium (Na) current, and four identical activation gates n for the Potassium (K) current.

Simulating an example Hodgkin-Huxley PDMP

GOAL

We are interested in implementing the Hodgkin-Huxley model described above with one hundred gates/doors of each time (m, h, and n).

As such, we will first implement the original model shown above, using m, h, and n as inputs to modulate the HHPDMP outputs. Then we will implement the example with 100 doors of each type.

METHOD

Setup:

We consider 3 types of doors m, h, and n such that:

- With t a given timestep, $\forall i \in \{m,h,n\},\ N^i$ is the number of doors X_t^i of type i
- Each door of type i has two states 0 and 1 with respective transition probabilities:

$$\begin{aligned}\forall i \in \{m,h,n\},\ \mathbb{P}_i(0 \to 1) &= \alpha_i(V_t)\\ \mathbb{P}_i(1 \to 0) &= \beta_i(V_t)\end{aligned}$$

We consider $\hat{m}_t$, $\hat{h}_t$, and $\hat{n}_t$ the respective proportion of open doors of each type such that:

$$\begin{aligned}\hat{m}_t &= \frac{1}{N^m}\sum_{i=1}^{N^m} X_t^{m,i}\\ \hat{h}_t &= \frac{1}{N^h}\sum_{i=1}^{N^h} X_t^{h,i}\\ \hat{n}_t &= \frac{1}{N^n}\sum_{i=1}^{N^n} X_t^{n,i}\end{aligned}$$

The regimes of a Hodgkin-Huxley PDMP corresponds to the *whole* state $\left(\frac{k^m}{N^m}, \frac{k^h}{N^h}, \frac{k^n}{N^n}\right)$ or $\left(\hat{m}_t, \hat{h}_t, \hat{n}_t\right)$ where $\forall i \in \{m,h,n\},\ k^i$ corresponds to the number of open doors (i.e. $X_t^i = 1$) The dynamics of $(\hat{V}_t)$ between the jumps is:

$$\begin{aligned}C_m\frac{d}{dt}\hat{V}_t &= -g_L(\hat{V}_t - E_L) - \bar{g}_{Na}(\frac{k^m}{N^m})^3\frac{k^h}{N^h}(\hat{V}_t - E_{Na}) - \bar{g}_K(\frac{k^n}{N^n})^4(\hat{V}_t - E_K)\\ &= -g_L(\hat{V}_t - E_L) - \bar{g}_{Na}(\hat{m}_t)^3\hat{h}_t(\hat{V}_t - E_{Na}) - \bar{g}_K(\hat{n}_t)^4(\hat{V}_t - E_K)\end{aligned}$$

The jumps for each type of door occur at rates:

$$\begin{aligned}\hat{m}^t \text{ jumps to } &\begin{cases}\hat{m}^t - \frac{1}{N^m} & \text{at rate } N^m\beta_m(\hat{V}_t)\hat{m}_t\\ \hat{m}^t + \frac{1}{N^m} & \text{at rate } N^m\alpha_m(\hat{V}_t)(1-\hat{m}_t)\end{cases}\\ \hat{h}^t \text{ jumps to } &\begin{cases}\hat{h}^t - \frac{1}{N^h} & \text{at rate } N^h\beta_h(\hat{V}_t)\hat{h}_t\\ \hat{h}^t + \frac{1}{N^h} & \text{at rate } N^h\alpha_h(\hat{V}_t)(1-\hat{h}_t)\end{cases}\\ \hat{n}^t \text{ jumps to } &\begin{cases}\hat{n}^t - \frac{1}{N^n} & \text{at rate } N^n\beta_n(\hat{V}_t)\hat{n}_t\\ \hat{n}^t + \frac{1}{N^n} & \text{at rate } N^n\alpha_n(\hat{V}_t)(1-\hat{n}_t)\end{cases}\end{aligned}$$

With rates $\alpha_m, \alpha_h, \alpha_n, \beta_m, \beta_h,$ and β_n as stated in the original paper:

$$\begin{aligned}\alpha_n &= 0{\cdot}01\ (V+10)\Big/\left(\exp\frac{V+10}{10}-1\right),\\ \beta_n &= 0{\cdot}125\ \exp\ (V/80),\\ \alpha_m &= 0{\cdot}1\ (V+25)\Big/\left(\exp\frac{V+25}{10}-1\right),\\ \beta_m &= 4\ \exp\ (V/18),\\ \alpha_h &= 0{\cdot}07\ \exp\ (V/20),\\ \beta_h &= 1\Big/\left(\exp\frac{V+30}{10}+1\right).\end{aligned}$$

(as previously stated)

Simulation method:

We rely on a so-called “rough algorithm” such that, given small time steps δ, we perform the following update at each time step:

$$\hat{V}_{t+\delta} \approx \hat{V}_t + \delta\frac{d\hat{V}_t}{dt}$$

Where:

$$\forall i \in \{m, h, n\},$$

$$N^i = 100$$

$$\hat{i}_{t+\delta} = \begin{cases} \hat{i}^t & \text{w/ proba. } 1 - \delta . N^i . \left[\beta_i(\hat{V}_t) . \hat{i}_t + \alpha_i(\hat{V}_t) . (1 - \hat{i}_t)\right] \\ \hat{i}^t - \frac{1}{N^i} & \text{w/ proba. } \delta . N^i . \beta_i(\hat{V}_t) . \hat{i}_t \\ \hat{i}^t + \frac{1}{N^i} & \text{w/ proba. } \delta . N^i . \alpha_i(\hat{V}_t) . (1 - \hat{i}_t) \end{cases}$$

$$\frac{d}{dt}\hat{V}_t = \frac{-g_L(\hat{V}_t - E_L) - \bar{g}_{Na}(\hat{m}_t)^3\hat{h}_t(\hat{V}_t - E_{Na}) - \bar{g}_K(\hat{n}_t)^4(\hat{V}_t - E_K)}{C_m}$$

And where the α and β rate functions are taken from the original paper along with the following parameters:

TABLE 3

Constant (1)	Value chosen (2)	Experimental values: Mean (3)	Experimental values: Range (4)	Reference (5)
C_M (μF/cm^2)	1·0	0·91	0·8 to 1·5	Table 1, Hodgkin *et al.* (1952)
V_{Na} (mV)	−115	−109	−95 to −119	p. 455, Hodgkin & Huxley (1952*a*)
V_K (mV)	+ 12	+ 11	+ 9 to + 14	Table 3, values for low temperature in sea water, Hodgkin & Huxley (1952*b*)
V_l (mV)	−10·613*	− 11	− 4 to − 22	Table 5, Hodgkin & Huxley (1952*b*)
$\bar{g}_{Na}$ (m.mho/cm^2)	120	80	65 to 90	Fully analysed results, Table 2† } Hodgkin & Huxley (1952*a*)
		160	120 to 260	Fresh fibres, p. 465† }
$\bar{g}_K$ (m.mho/cm^2)	36	34	26 to 49	p. 463, Hodgkin & Huxley (1952*a*)
$\bar{g}_l$ (m.mho/cm^2)	0·3	0·26	0·13 to 0·50	Table 5, Hodgkin & Huxley (1952*b*)

* Exact value chosen to make the total ionic current zero at the resting potential ($V = 0$).

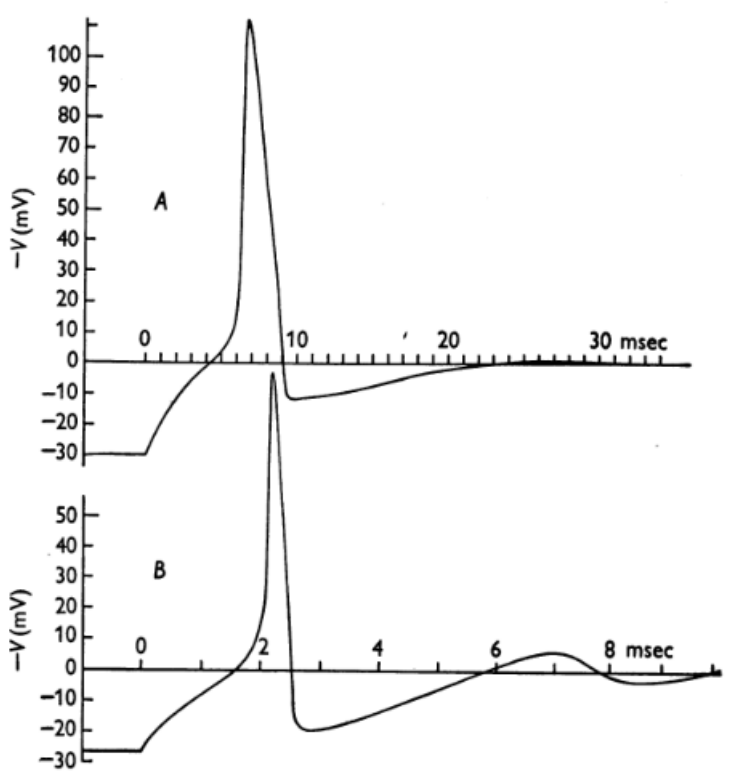
† The experimental values for $\bar{g}_{Na}$ were obtained by multiplying the peak sodium conductances by factors derived from the values chosen for α_m, β_m, α_h, and β_h.

Function implementations:

```
# Declares all intermediary rate functions alpha_i and beta_i

# Alpha and Beta rate function from original paper
am <- function(V) 0.1*(V+25)/(exp((V+25)/10)-1)
ah <- function(V) 0.07*exp(V/20)
an <- function(V) 0.01*(V+10)/(exp((V+10)/10)-1)
bm <- function(V) 4*exp(V/18)
bh <- function(V) 1/(exp((V+30)/10)+1)
bn <- function(V) 0.125*exp(V/80)

# Declares the V-differential function
dvdt <- function(V, Vl, Vna, Vk, gl, gna, gk, m, h, n, C) {
  -1/C * (gl*(V-Vl) + gna*m^3*h*(V-Vna) + gk*n^4*(V-Vk))
}

# Declares a generic function to update m, h, or n
update <- function(i, Ni, V, alpha, beta, delta) {
  # Draws uniformly a RV, and computes the jump probabilities
  proba_down   = Ni*beta(V)*i*delta
  proba_up     = Ni*alpha(V)*(1-i)*delta
  uniform_draw = runif(1, 0, 1)
  # Checks whether a jump occurs or not
  if (uniform_draw <= proba_down) {
    return(i - 1/Ni)
  } else if (uniform_draw <= proba_down + proba_up) {
    return(i + 1/Ni)
  } else {
    return(i)
  }
}

hodgkin_huxley_PDMP <- function(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr=0
) {
  ### Hudgkin Huxley PDMP function using a rough algorithm
  ### relying on jump probabilities at given small timesteps delta
  # Declares the return space
  V = + V - Vr # negative depolarization in mV
  interval = matrix(seq(0, time_length, timestep))
  V_seq    = matrix(rep(V, length(interval)))
  m_seq    = matrix(rep(m, length(interval)))
  h_seq    = matrix(rep(h, length(interval)))
  n_seq    = matrix(rep(n, length(interval)))
  # Performs the iterative update per timestep
  for (i in 2:length(interval)) {
    # Updates m, h, and n
    m_seq[i] = update(m_seq[i-1,], Nm, V_seq[i-1,], am, bm, timestep)
    h_seq[i] = update(h_seq[i-1,], Nh, V_seq[i-1,], ah, bh, timestep)
    n_seq[i] = update(n_seq[i-1,], Nn, V_seq[i-1,], an, bn, timestep)
    # Updates V
    V_seq[i] = V_seq[i-1,] + timestep*dvdt(
      V_seq[i-1,], Vl, Vna, Vk, gl, gna, gk,
      m_seq[i,], h_seq[i,], n_seq[i,], C
    )
  }
  # Plots the resulting simulation
  par(mfrow = c(2, 2), mar=c(2.8,2.5,2.5,2), mgp=c(1.8, 0.75, 0))
  # OF NOTE: the paper displays the V values as its negative
  # see example graph page 537 here:
  # https://physiology.arizona.edu/sites/default/files/hodgkinhuxley1952_0.pdf
  plot(interval, -V_seq, type="l", col='red',
```

```
      xlab="mS", ylab="-V(mV)")
  plot(interval, m_seq, type="l", col='blue',
      xlab="mS", ylab="Proportion open m gates")
  plot(interval, h_seq, type="l", col='green',
      xlab="mS", ylab="Proportion open h gates")
  plot(interval, n_seq, type="l", col='purple',
      xlab="mS", ylab="Proportion open n gates")
  title = paste("Simulation results over", time_length, "(milliseconds)\n",
                "with a timestep of", timestep, "(milliseconds)")
  mtext(title, side = 1, line = -29, outer=TRUE)
  # Returns
  return(list(
    "timesteps"=interval,
    "V"=V_seq, "-V"=-V_seq,
    "m"=m_seq, "h"=h_seq, "n"=n_seq
    )
  )
}
```

Of note, up until now, we have shown the modeling of V (in microVolt mV). In the original paper, the authors then switch to data visualizing the modeling of V via its inverse $-V$ such as in page 537 here (https://physiology.arizona.edu/sites/default/files/hodgkinhuxley1952_0.pdf) and reproduced below:



As such, the function declared above returns both V and $-V$ but will only display graphically the latter to keep with the original paper's format.

RESULTS - Simulation with the Rough algorithm

Declaring the general parameter space:

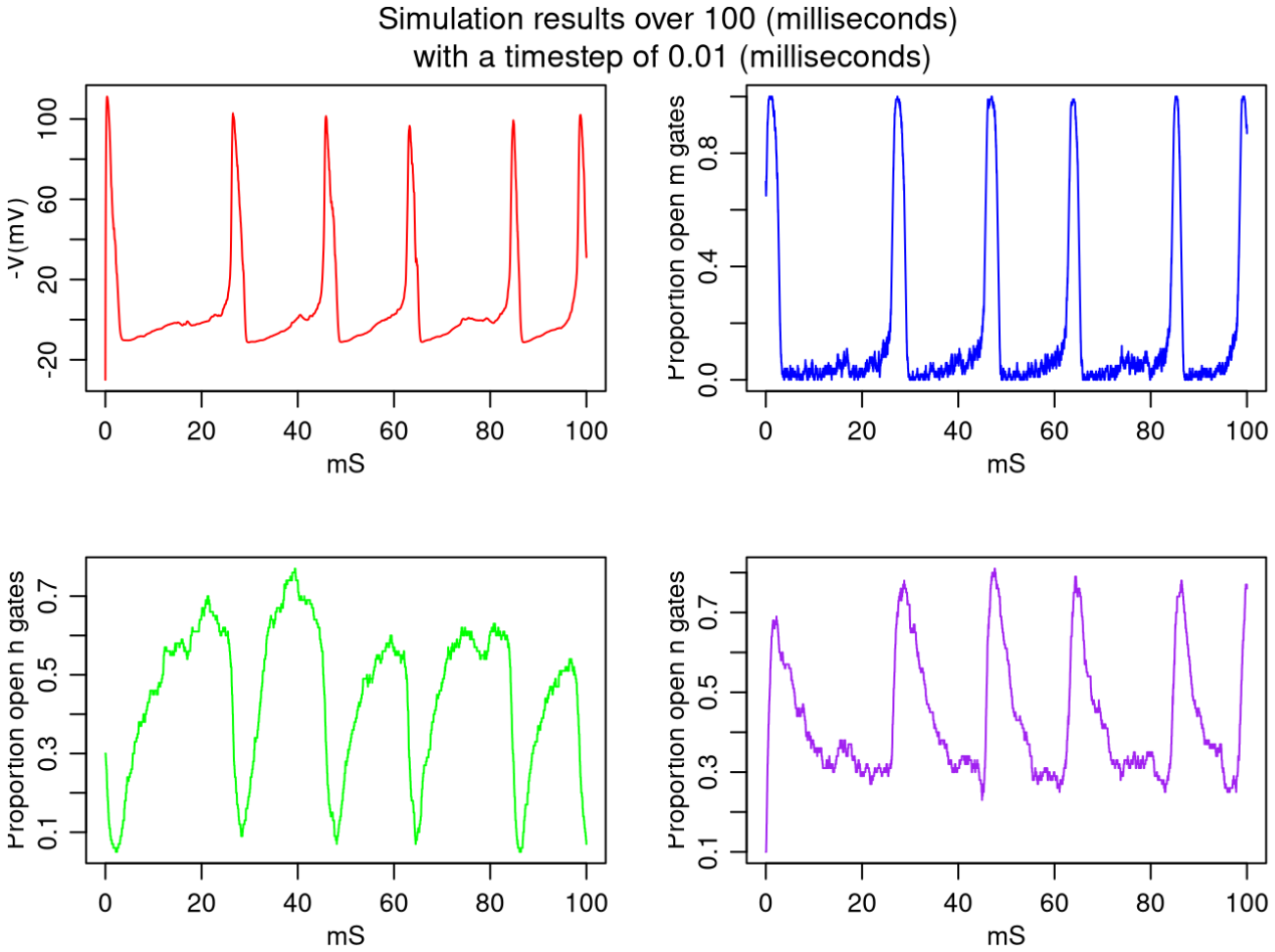
Parameters	Value	Note
length	100	milliseconds
timestep δ	0.01	milliseconds
C_m	1	*taken from original paper*
V_l	-10.615	*taken from original paper*
V_{Na}	-115	*taken from original paper*
V_k	12	*taken from original paper*

Parameters	Value	Note
m	0.7	arbitrary choice
h	0.3	arbitrary choice
n	0.1	arbitrary choice
g_l	0.3	*taken from original paper*
g_{Na}	120	*taken from original paper*
g_k	36	*taken from original paper*
Nm	100	arbitrary choice
Nh	100	arbitrary choice
Nn	100	arbitrary choice
V	30	*taken from original paper*
V_r	0	*taken from original paper*

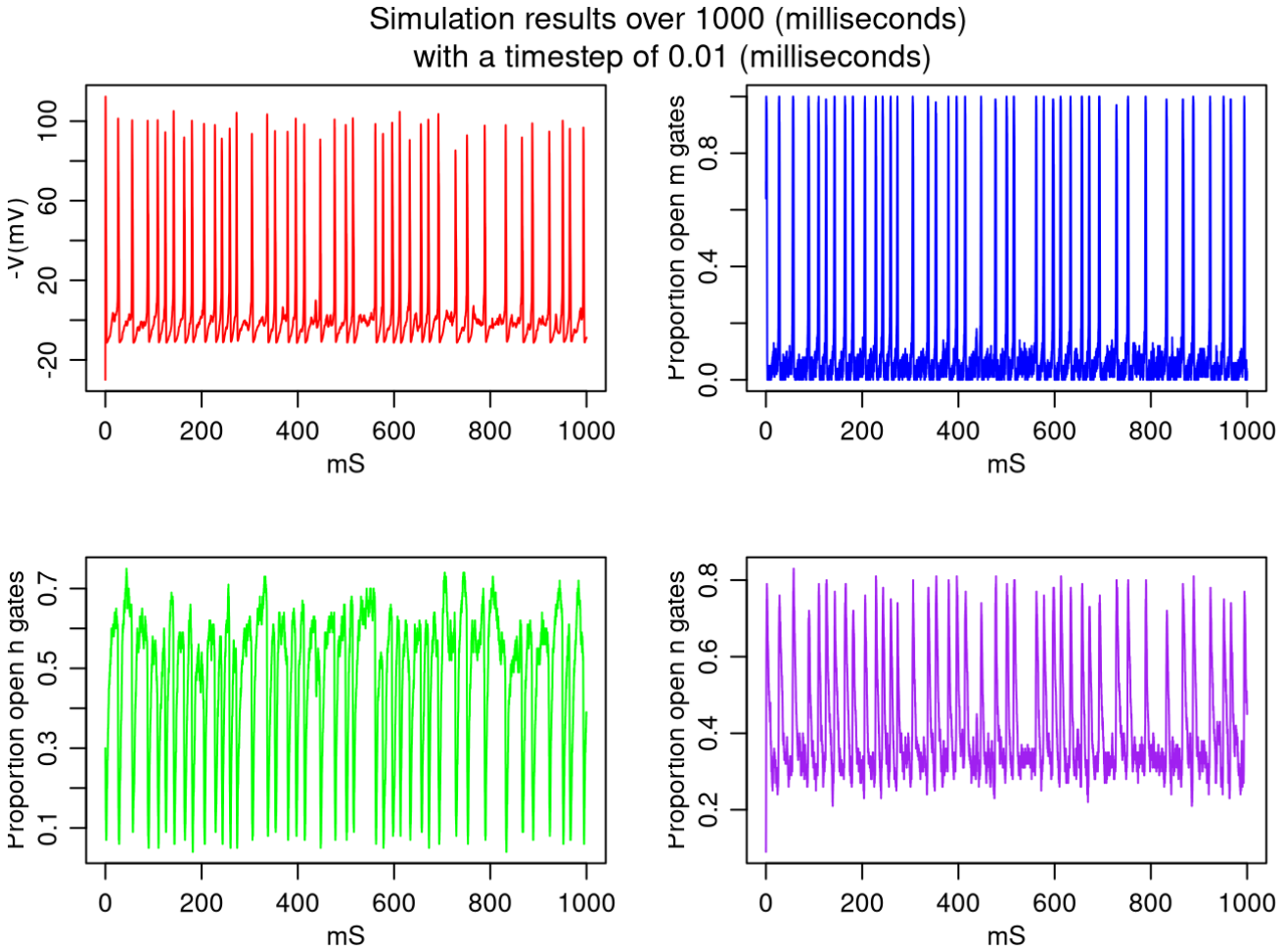
```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
C           = 1       # paper OG value (resting potential 0)
# Conductance levels
Vl          = -10.613 # paper OG value (resting potential 0)
Vna         = -115    # paper OG value (resting potential 0)
Vk          = 12      # paper OG value (resting potential 0)
# Initial open proportions
m           = 0.7     # arbitrary choice
h           = 0.3     # arbitrary choice
n           = 0.1     # arbitrary choice
# Conductance values
gl          = 0.3     # paper OG value (resting potential 0)
gna         = 120     # paper OG value (resting potential 0)
gk          = 36      # paper OG value (resting potential 0)
# number of doors
Nm          = 100     # arbitrary choice
Nh          = 100     # arbitrary choice
Nn          = 100     # arbitrary choice
# Membrane displacement potential (negative depolarization)
V           = 30      # arbitrary choice (original paper has V starting around 30)
# For V, see page 536 here:
# https://physiology.arizona.edu/sites/default/files/hodgkinhuxley1952_0.pdf
Vr          = 0       # paper OG value (resting potential 0)
```

Varying the timelength with a given timestep of 0.01:

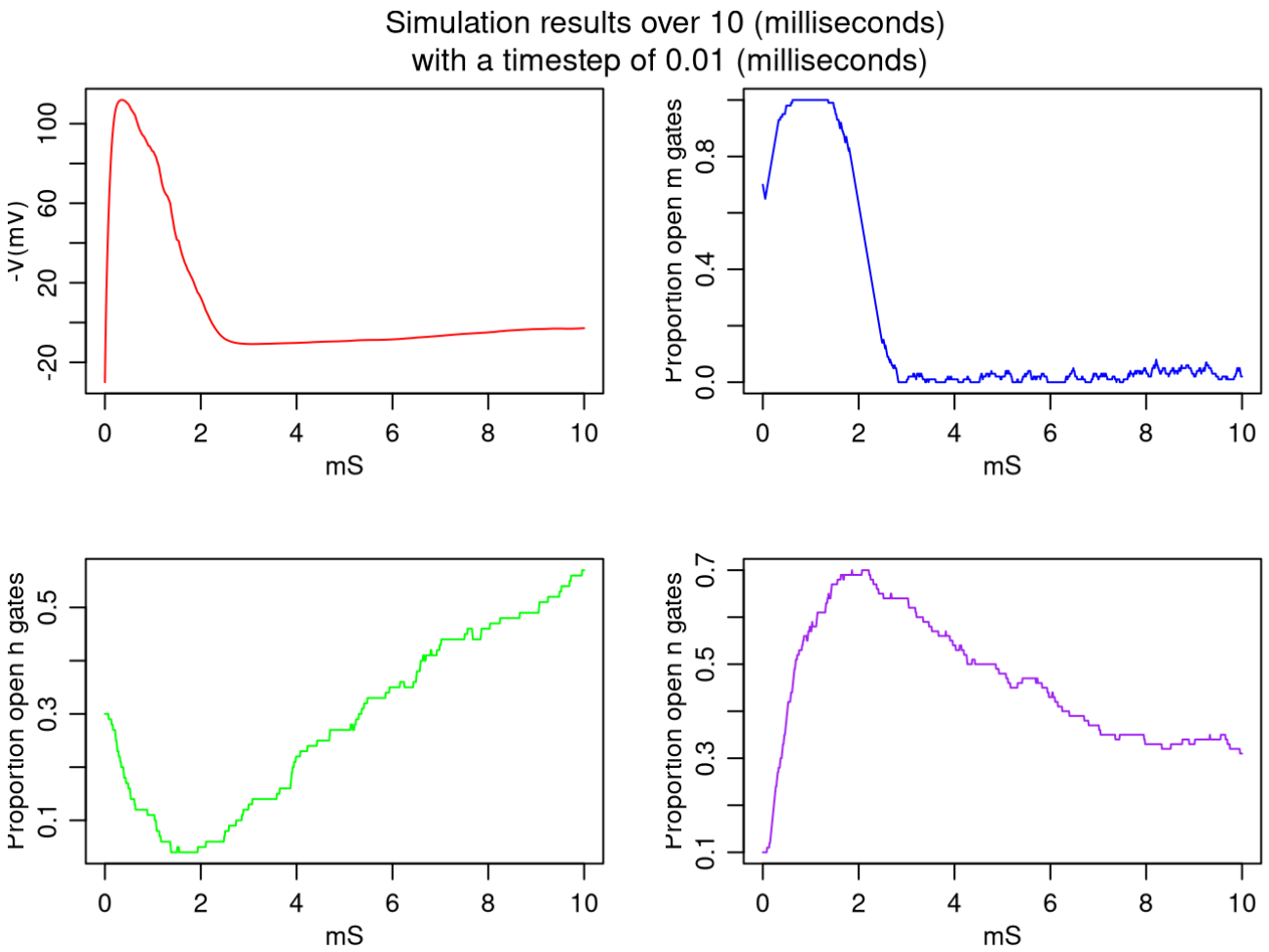
```
simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```




```
# Declares parameters
time_length = 1000 # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

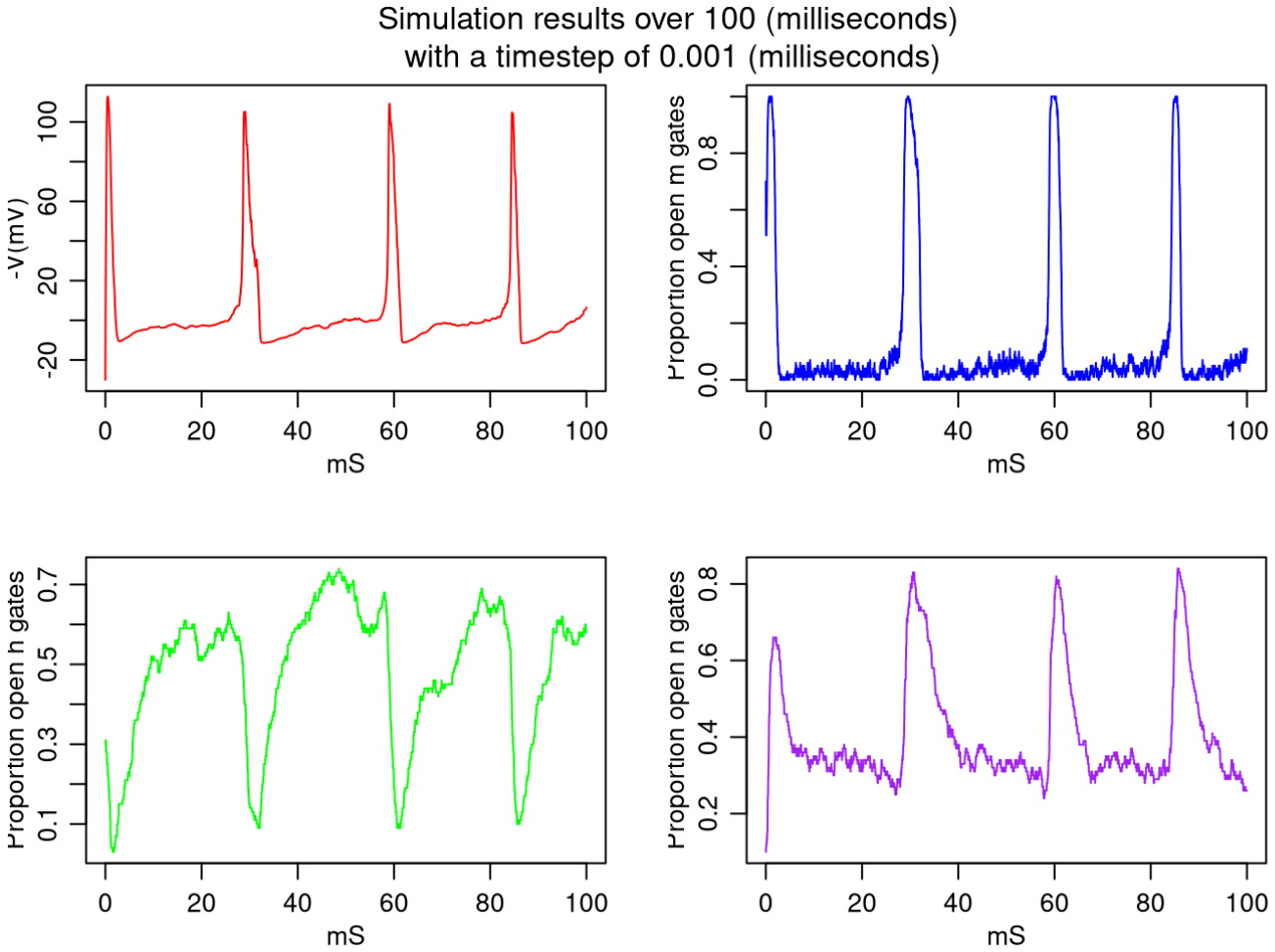



```
# Declares parameters
time_length = 10 # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

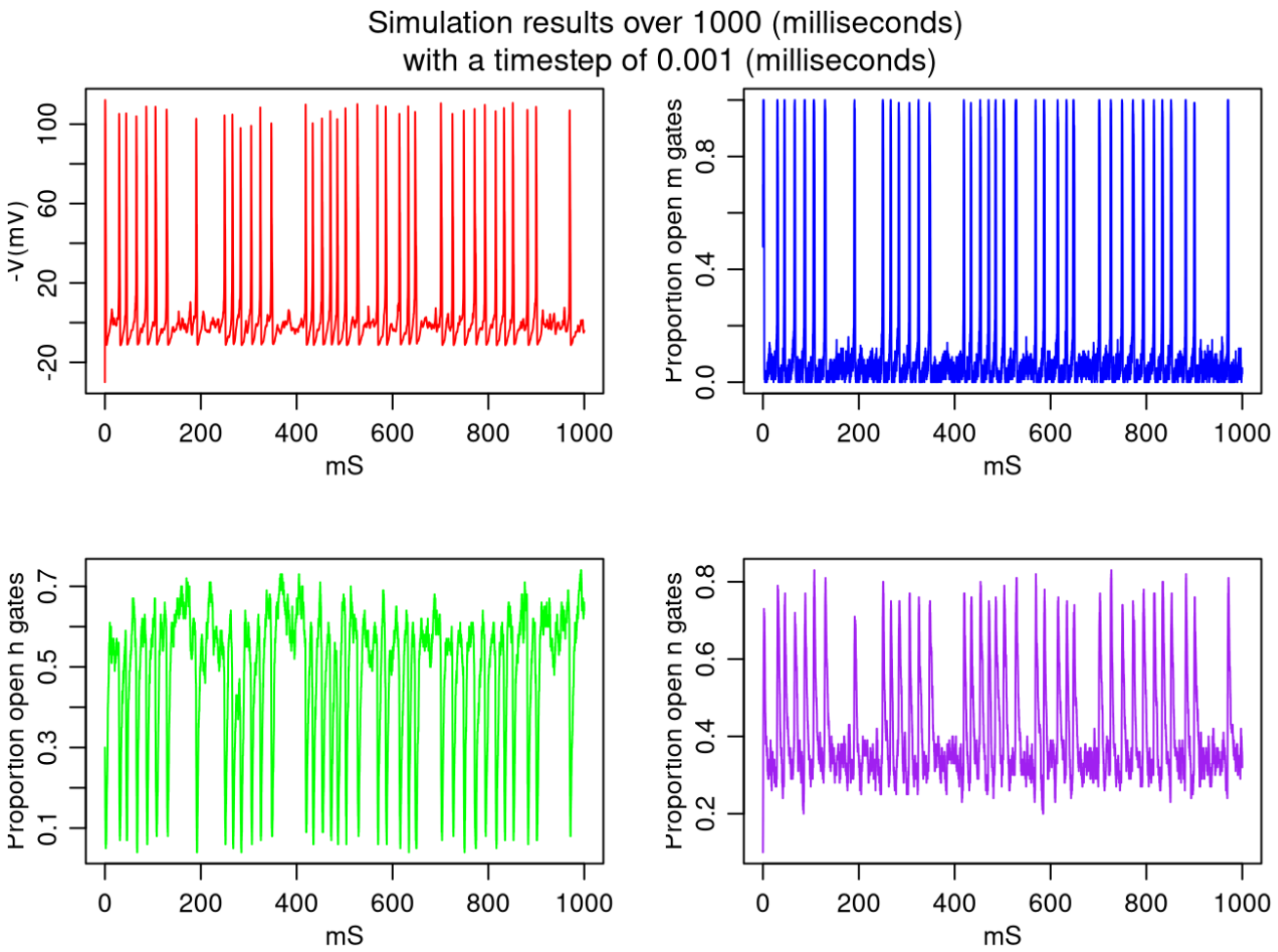


Varying the timelength with a given timestep of 0.001:

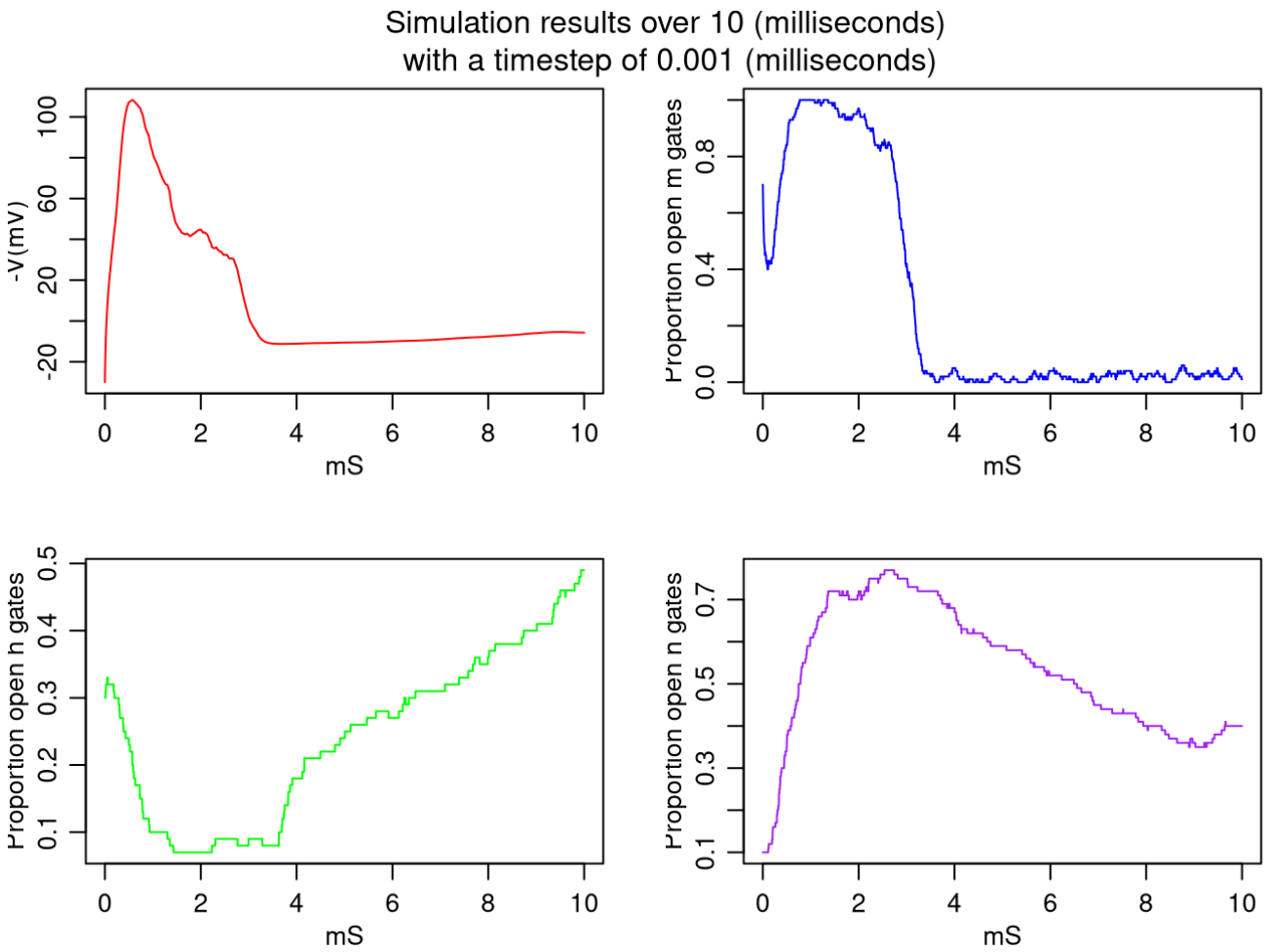
```
# Declares parameters
time_length = 100   # arbitrary choice
timestep    = 0.001 # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```




```
# Declares parameters
time_length = 1000  # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

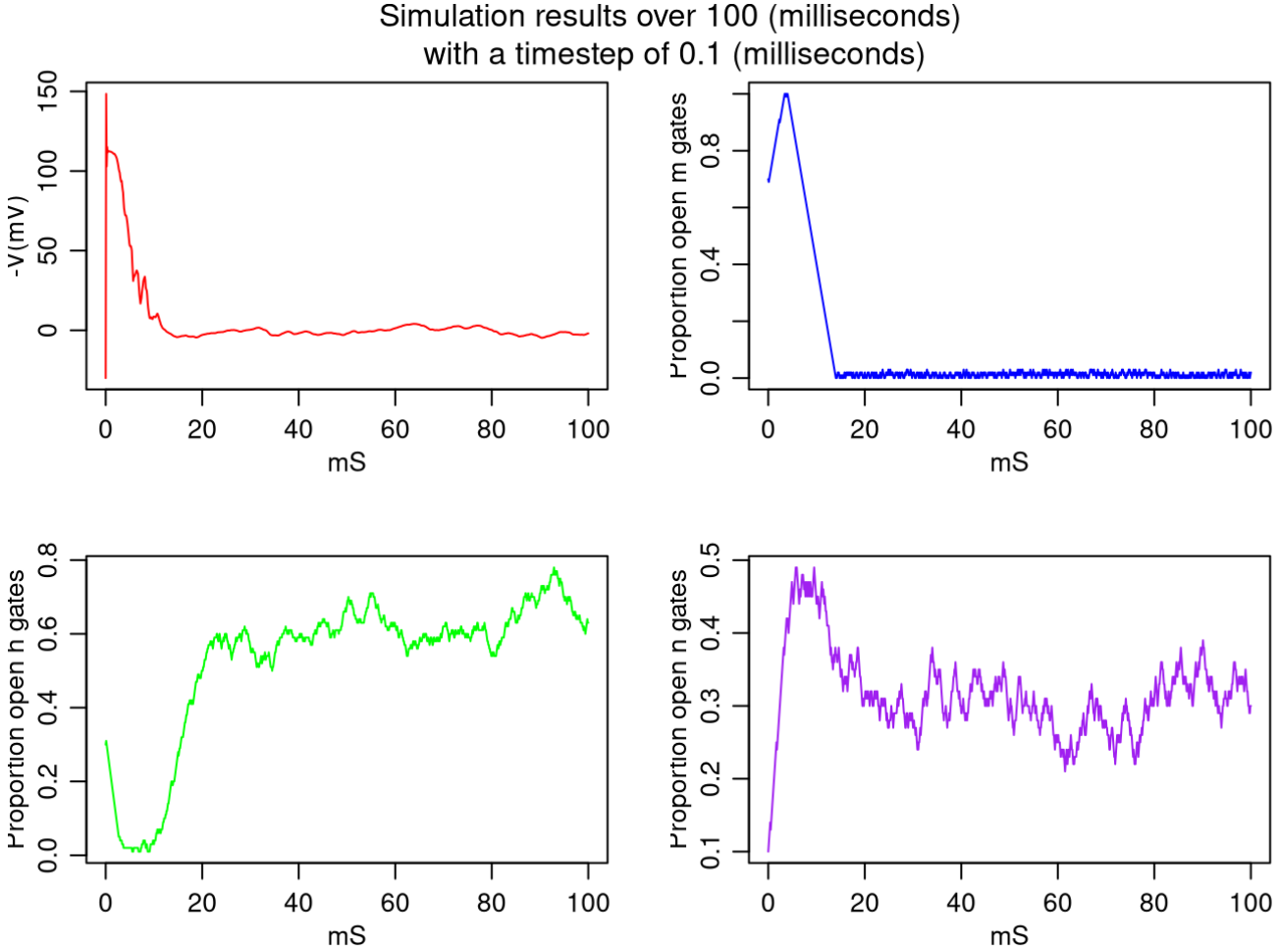



```
# Declares parameters
time_length = 10    # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

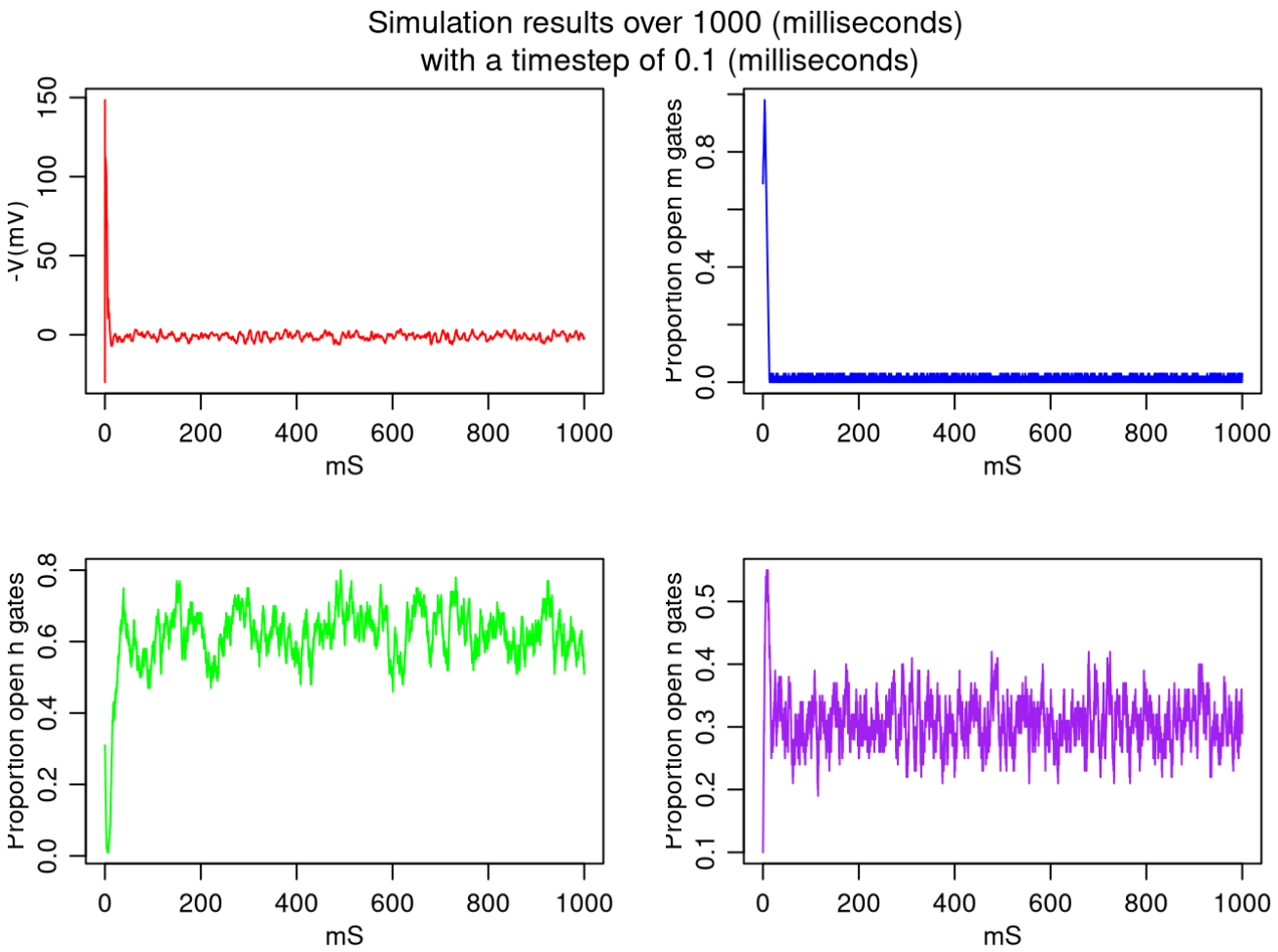


Varying the timelength with a given timestep of 0.1:

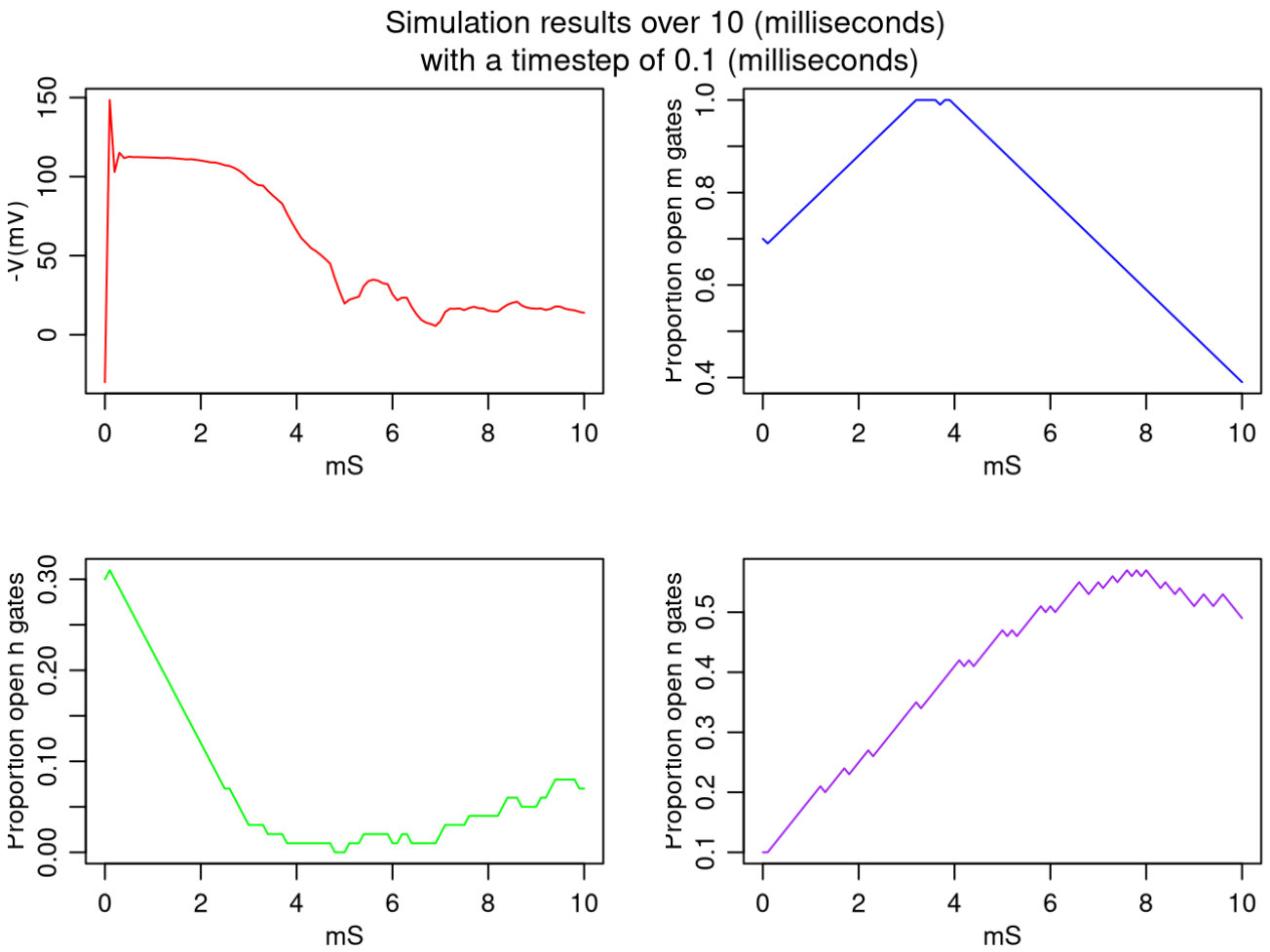
```
# Declares parameters
time_length = 100   # arbitrary choice
timestep    = 0.1 # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```




```
# Declares parameters
time_length = 1000   # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

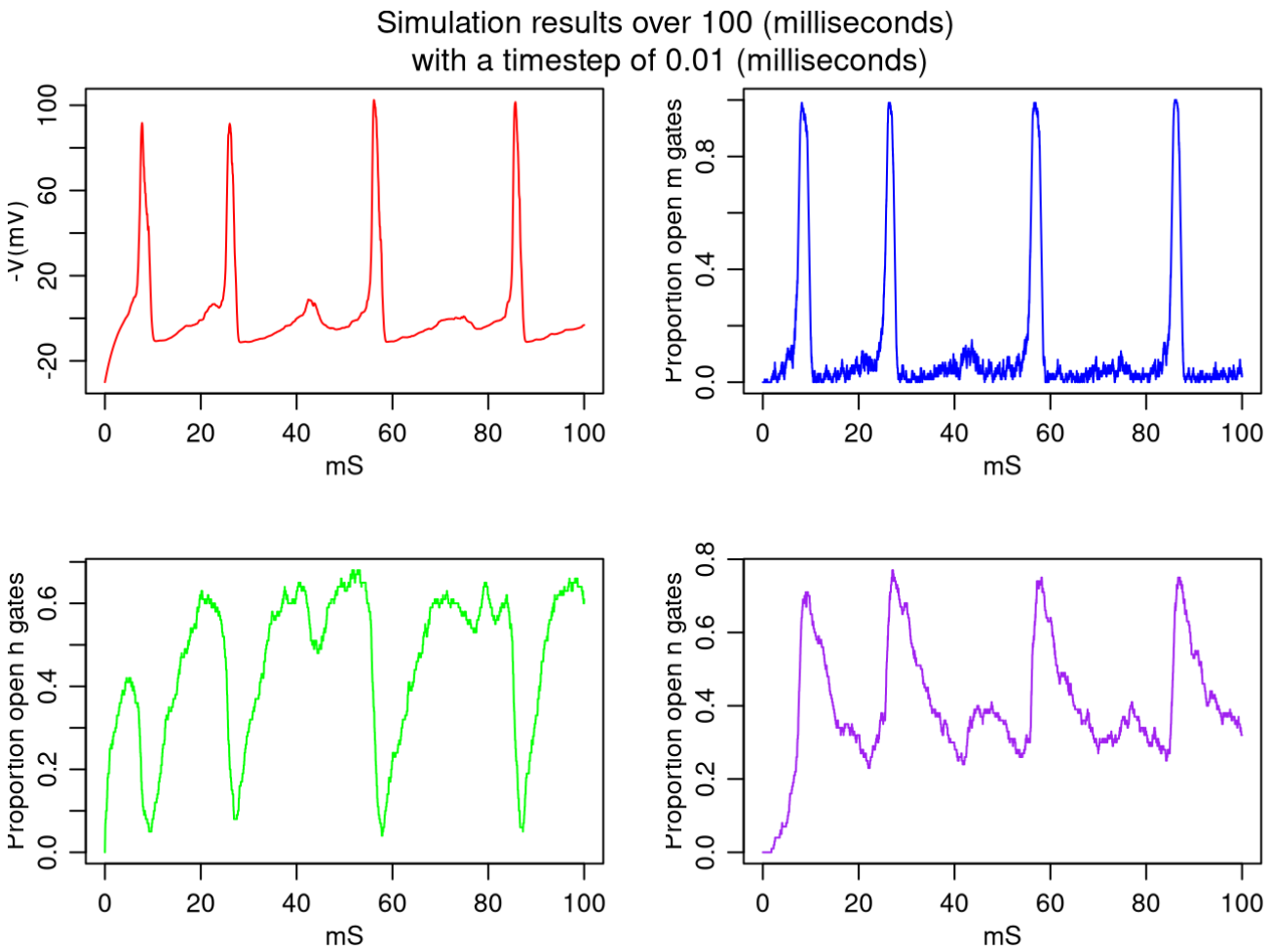



```
# Declares parameters
time_length = 10   # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```

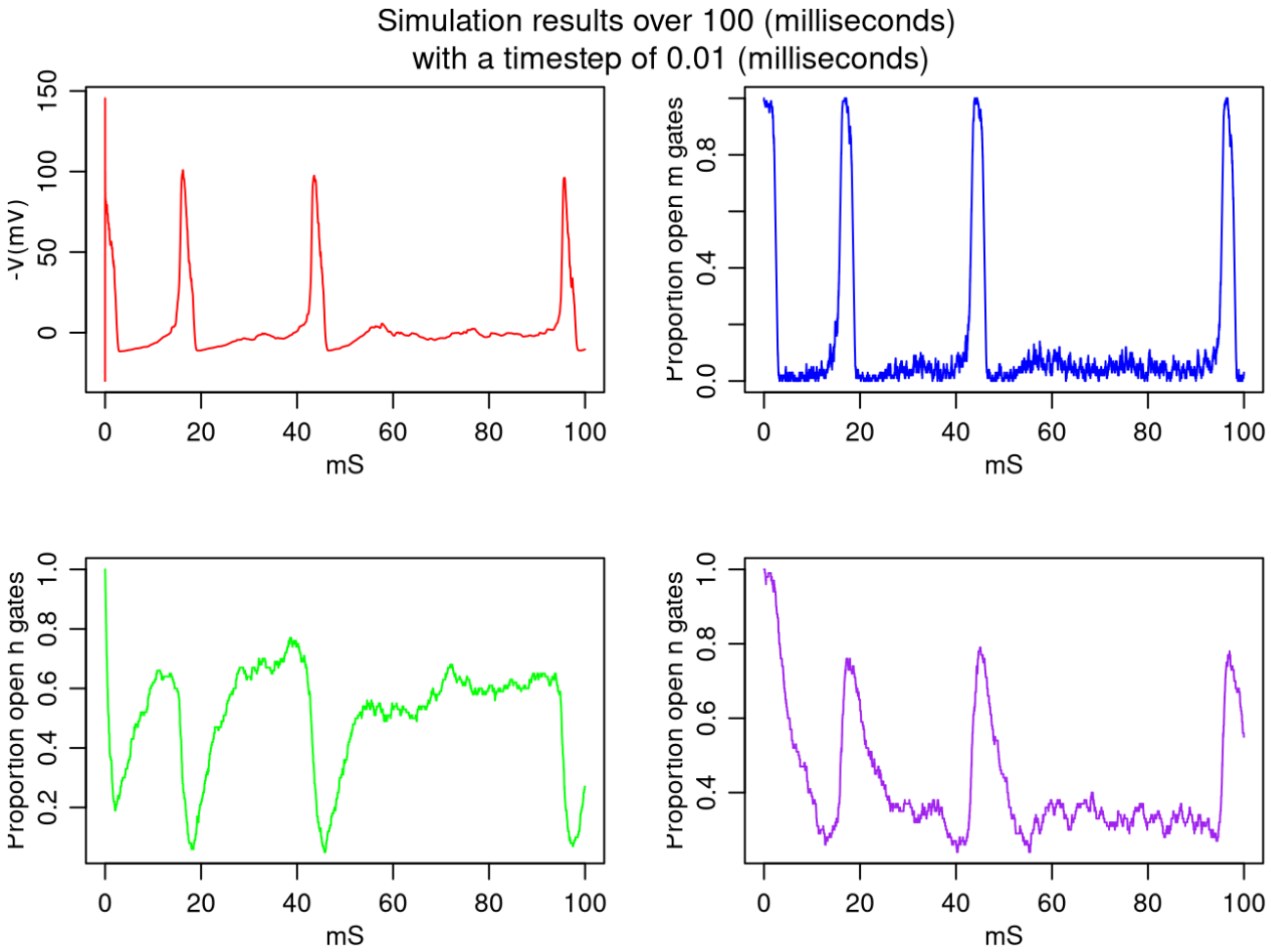


Varying gate conductance parameters:

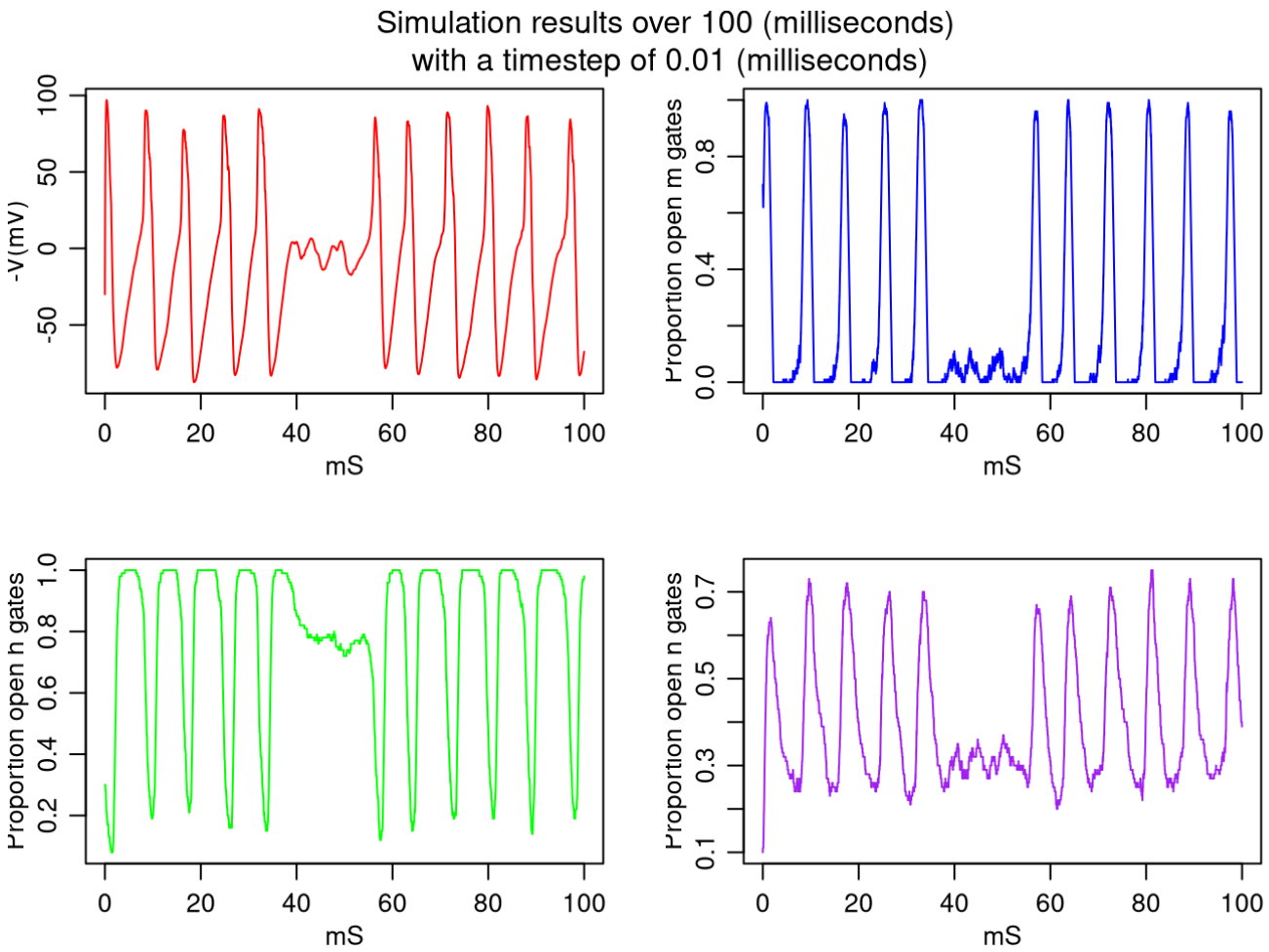
```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
# Initial open proportions
m           = 0    # arbitrary choice
h           = 0    # arbitrary choice
n           = 0    # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```



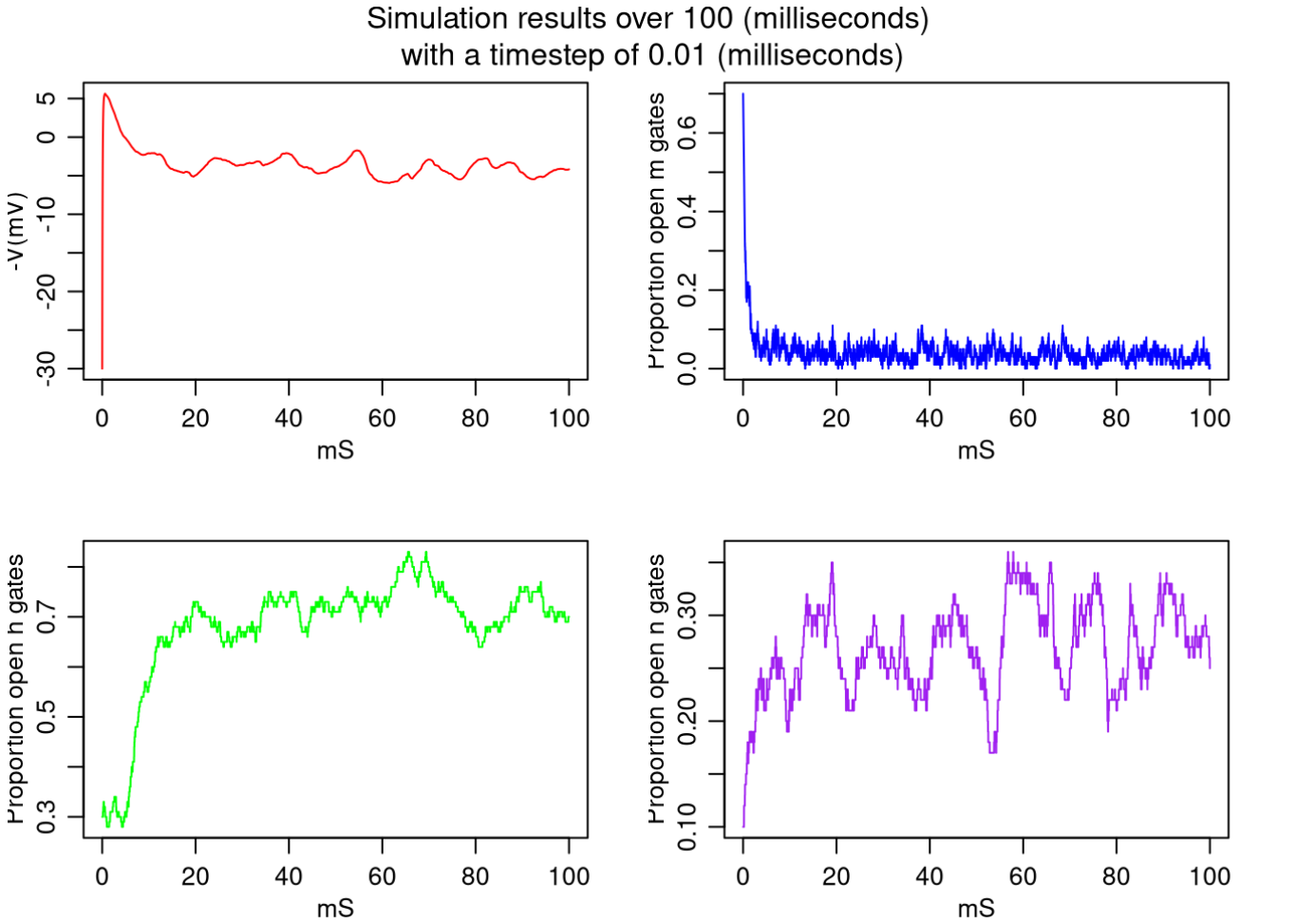

```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
# Initial open proportions
m           = 1    # arbitrary choice
h           = 1    # arbitrary choice
n           = 1    # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```



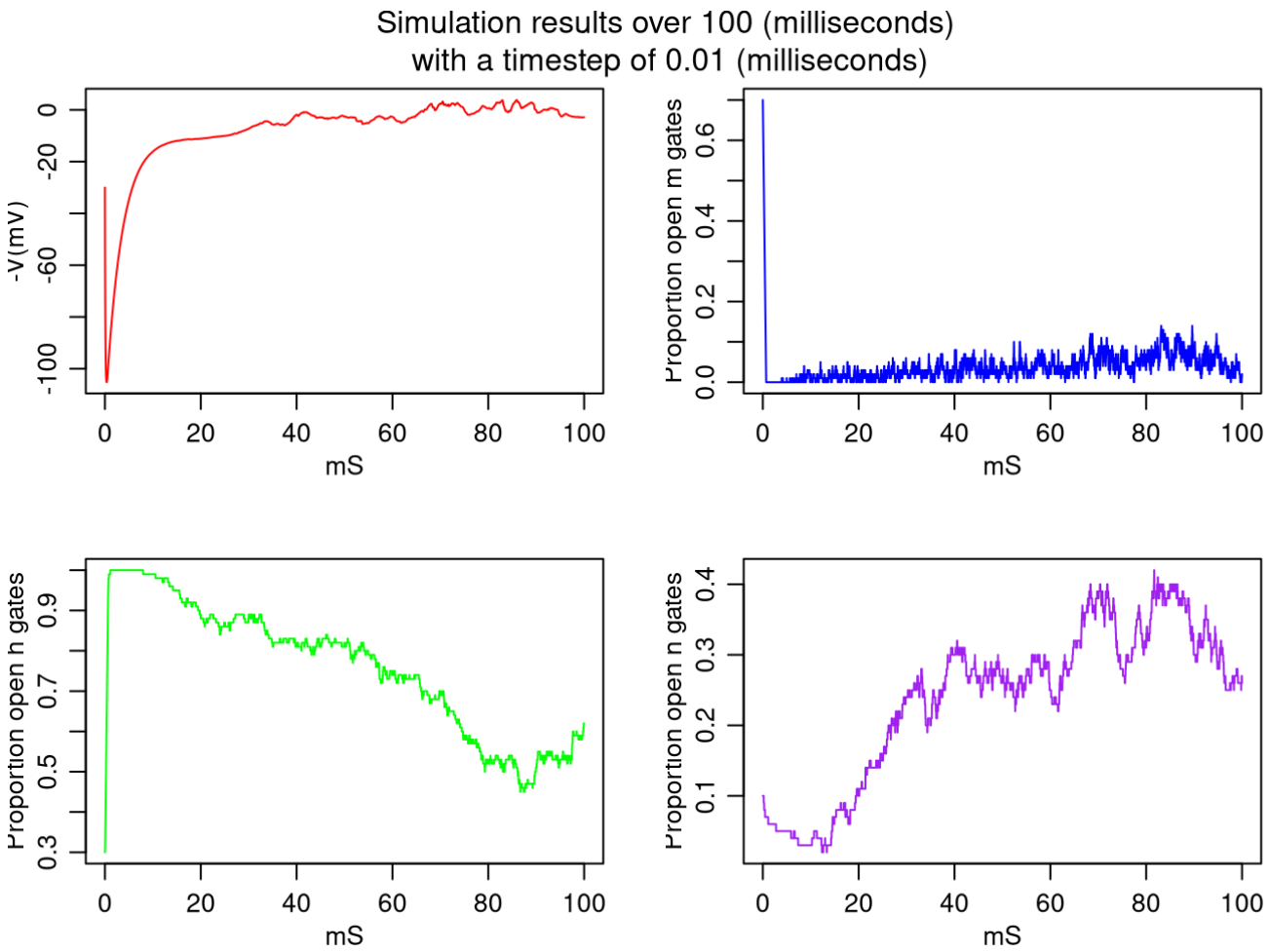

```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
# Initial open proportions
m           = 0.7     # arbitrary choice
h           = 0.3     # arbitrary choice
n           = 0.1     # arbitrary choice
# Conductance levels
Vl          = -100
Vna         = -100
Vk          = 100

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```




```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
# Conductance levels
Vl          = 0       # arbitrary choice
Vna         = -10     # arbitrary choice
Vk          = 10      # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```




```
# Declares parameters
time_length = 100     # arbitrary choice
timestep    = 0.01    # arbitrary choice
# Conductance levels
Vl          = 10.613  # arbitrary choice
Vna         = 115     # arbitrary choice
Vk          = -12     # arbitrary choice

simulation = hodgkin_huxley_PDMP(
  time_length, timestep,
  C,
  Vl, Vna, Vk,
  m, h, n,
  gl, gna, gk,
  Nm, Nh, Nn,
  am, ah, an, bm, bh, bn,
  V, Vr
)
```



COMMENTS

Starting with the following baseline set of parameters:

Parameters	Value	Note
length	100	milliseconds
timestep δ	0.01	milliseconds
C_m	1	*taken from original paper*
V_l	-10.615	*taken from original paper*
V_{Na}	-115	*taken from original paper*
V_k	12	*taken from original paper*
m	0.7	arbitrary choice
h	0.3	arbitrary choice
n	0.1	arbitrary choice
g_l	0.3	*taken from original paper*
g_{Na}	120	*taken from original paper*
g_k	36	*taken from original paper*
Nm	100	arbitrary choice
Nh	100	arbitrary choice
Nn	100	arbitrary choice
V	30	*taken from original paper*
V_r	0	*taken from original paper*

We can observe the following:

- Given a simulation timestep δ of 0.01 or 0.001 milliseconds, we find that we have, in general, a simulated spike every 20 to 30 milliseconds.
- Increasing the timestep δ to 0.1 milliseconds alters the behavior of the rough simulation – indicating that the function might not work at high timestep resolutions:
  - Only one spike is generated
  - The spike's shape differs from other setups with a smaller/finer δ
- Given a simulation timestep δ of 0.01 and a simulated length of 100 milliseconds, we find:
  - Setting the initial proportions m, h, and n to either 0 or 1 does not seem to affect the general behavior of the simulation after a few steps as the proportions' behavior seem to converge back to what was observed in the very first simulation
  - Modifying the ion capacitance V_l, V_{Na}, and V_k: strongly affects the simulation's behavior
    - Increasing each value V_l, V_k, V_{Na} by an order of magnitude seems to double or triple the number of generated spikes
    - Reducing these values or nullifying them leads to an absence of spikes and a capacitance V hovering around 0
    - Inverting the values V_l, V_k, V_{Na} as stated in the original paper also leads to an absence of spikes and a capacitance V converging towards 0

IMPLEMENTATION OF THE DIFFERENTIAL MODEL WITH THE SIMECOL LIBRARY

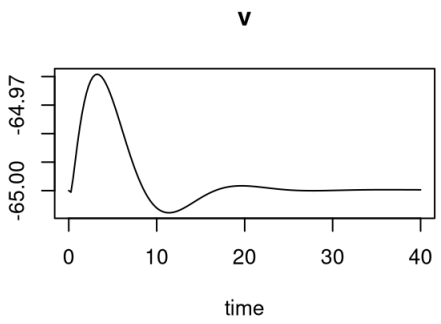
Exported from the R-bloggers (https://www.r-bloggers.com/2012/06/hodgkin-huxley-model-in-r/) website, it is possible to perform a Hodgkin-Huxley dynamic simulation (here with Ordinary Differential Equations (ODE) from the simecol library (http://simecol.r-forge.r-project.org/)).

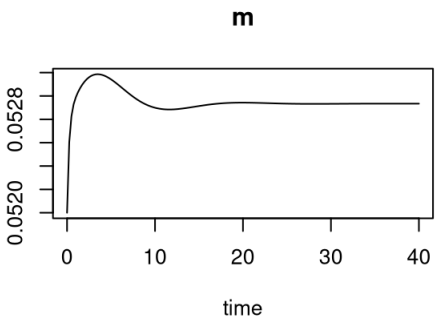
We note that the provided rate functions α and β differs from the original paper.

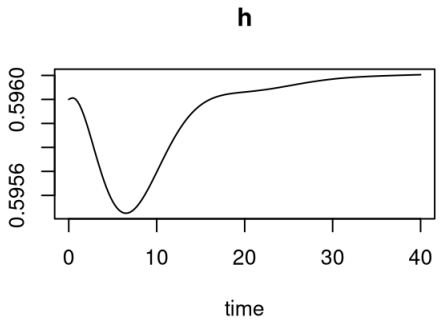
```
# install.packages("simecol")
library(simecol)
```

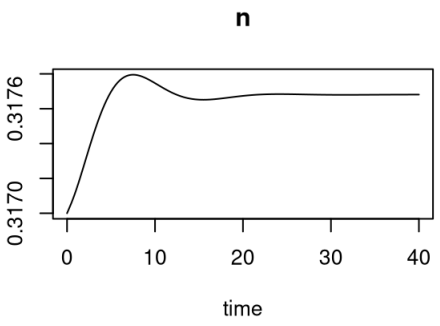
```
## Hodkin-Huxley model
HH <- odeModel(
main = function(time, init, parms) {
  with(as.list(c(init, parms)),{

    am <- function(v) 0.1*(v+40)/(1-exp(-(v+40)/10))
    bm <- function(v) 4*exp(-(v+65)/18)
    ah <- function(v) 0.07*exp(-(v+65)/20)
    bh <- function(v) 1/(1+exp(-(v+35)/10))
    an <- function(v) 0.01*(v+55)/(1-exp(-(v+55)/10))
    bn <- function(v) 0.125*exp(-(v+65)/80)

    dv <- (I - gna*h*(v-Ena)*m^3-gk*(v-Ek)*n^4-gl*(v-El))/C
    dm <- am(v)*(1-m)-bm(v)*m
    dh <- ah(v)*(1-h)-bh(v)*h
    dn <- an(v)*(1-n)-bn(v)*n

    return(list(c(dv, dm, dh, dn)))
  })
  },
  ## Set parameters
  parms = c(Ena=50, Ek=-77, El=-54.4, gna=120, gk=36, gl=0.3, C=1, I=0),
  ## Set integrations times
  times = c(from=0, to=40, by = 0.25),
  ## Set initial state
  init = c(v=-65, m=0.052, h=0.596, n=0.317),
  solver = "lsoda"
)
```

```
HH <- sim(HH)
plot(HH)
```


v
-64.97
-65.00
0
10
20
30
40
time


m
0.0528
0.0520
0
10
20
30
40
time


h
0.5960
0.5956
0
10
20
30
40
time


n
0.3176
0.3170
0
10
20
30
40
time