In [1]:
```python
import numpy as np
import matplotlib.pyplot as plt
```

In [2]:
```python
def get_timeline(t_max, dt):
    return np.arange(0, t_max, dt)
```

1. Hodgkin-Huxley model of action potential generation.

In [3]:
```python
def initialize_arrays(t,initial_values) :
    n = np.zeros(len(t))
    m = np.zeros(len(t))
    h = np.zeros(len(t))
    i_k = np.zeros(len(t))
    i_na = np.zeros(len(t))
    i_leak = np.zeros(len(t))
    v = np.zeros(len(t))

    n[0] = initial_values['n0']
    m[0] = initial_values['m0']
    h[0] = initial_values['h0']
    v[0] = initial_values['v0']

    return n, m, h, i_k, i_na, i_leak, v
```

In [4]:
```python
def euler(f_func, t_max, dt, params, initial_values):
    t = get_timeline(t_max, dt)

    n, m, h, i_k, i_na, i_leak, v = initialize_arrays(t, initial_values)

    i_e = exp_applied_current(params, t)

    for i in range(len(t)-1):
        n[i+1] = n[i] + open_close_ion_channel_probability(alpha_n, beta_n, v[i], n[i])*dt
        m[i+1] = m[i] + open_close_ion_channel_probability(alpha_m, beta_m, v[i], m[i])*dt
        h[i+1] = h[i] + open_close_ion_channel_probability(alpha_h, beta_h, v[i], h[i])*dt

        i_k[i+1] = potassium_current(v[i], n[i])
        i_na[i+1] = sodium_current(v[i], m[i], h[i])
        i_leak[i+1] = leak_current(v[i])

        v[i+1] = v[i] + f_func(v[i], i_k[i+1], i_na[i+1], i_leak[i+1], i_e[i], params['c_m'])*dt
    return n, m, h, i_k, i_na, i_leak, v, t
```

In [5]:
```python
def alpha_n(v) :
    return 0.01*(v + 55)/(1 - np.exp(-0.1 * (v + 55)))
```

In [6]:
```python
def beta_n(v) :
    return 0.125 * np.exp(-0.0125 * (v + 65))
```

In [7]:
```python
def alpha_m(v) :
    return 0.1*(v + 40)/(1 - np.exp(-0.1 * (v + 40)))
```

In [8]:
```python
def beta_m(v) :
    return 4 * np.exp(-0.0556 * (v + 65))
```

In [9]:
```python
def alpha_h(v) :
    return 0.07 * np.exp(-0.05 * (v + 65))
```

In [10]:
```python
def beta_h(v) :
    return 1/(1 + np.exp(-0.1 * (v + 35)))
```

In [11]:
```python
def open_close_ion_channel_probability(alpha_func, beta_func, v, x) :
    return alpha_func(v)*(1-x) - beta_func(v)*x
```

In [12]:
```python
def open_close_ion_channel_probability_m(m, t, params) :
    return alpha_m(params['v'])*(1-m) - beta_m(params['v'])*m
```

In [13]:
```python
def open_close_ion_channel_probability_h(h, t, params) :
    return alpha_h(params['v'])*(1-h) - beta_h(params['v'])*h
```

In [14]:
```python
# 1 Seimens = 1 Ampere/Volt = 1/1000 A/mV
# in our problem, voltages is in mV, thus if we use conductance in Seimens, the current will be in (10^-3)A
```

In [15]:
```python
def potassium_current(v, n) :
    g_k = 36 * 1e-9 #S
    e_k = -77  #mV
    return g_k * np.power(n,4) * (v - e_k) * 1e-3 # current in A
```

In [16]:
```python
def sodium_current(v, m, h) :
    g_na = 120*1e-9 #S
    e_na = 50 #mV
    return g_na * np.power(m,3) * h * (v - e_na) * 1e-3 # current in A
```

In [17]:
```python
def leak_current(v) :
    g_leak = 0.3 * 1e-9 #S
    e_leak =-54.387 #mV
    return g_leak * (v - e_leak) * 1e-3 # current in A
```

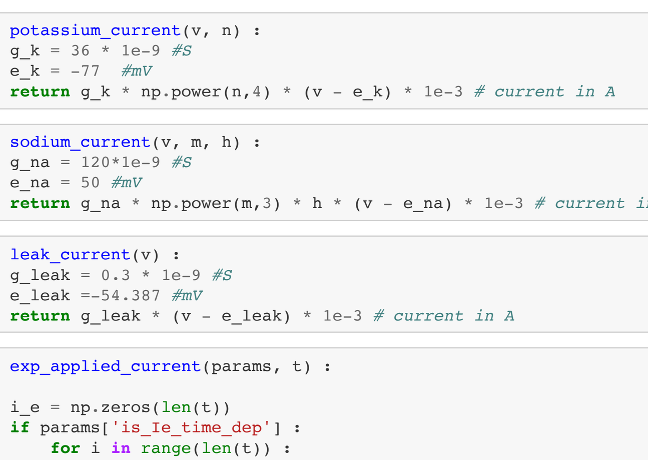
In [18]:
```python
def exp_applied_current(params, t) :

    i_e = np.zeros(len(t))
    if params['is_Ie_time_dep'] :
        for i in range(len(t)) :
            if(t[i] <= params['current_pulse_length']) :
                i_e[i] = params['ie']
    elif params['is_Ie_sinusoidal'] :
        i_e = (2*1e-12) * np.sin(2 * np.pi * params['freq'] * (t * 1e-3)) # time in seconds
    else:
        i_e.fill(params['ie'])

    return i_e
```

1 (a) Simulate the Hodgkin-Huxley model by numerically

In [19]:
```python
def hodgkin_huxley_model(v, i_k, i_na, i_leak, i_e, c_m) :
    i = (- i_na - i_k - i_leak + i_e)*1e-9 # in nA
    c_m = c_m*1e-12
    potential = (- i_na - i_k - i_leak + i_e)/c_m # in volt/sec = mV/ms
    return potential # in mV/ms
```

In [20]:
```python
dt = 1e-2 # in ms
t_max = 50 #(in ms) as per the sample graph

initial_values = {
    'v0' : -65,
    'n0' : 0.3177,
    'm0' : 0.0529,
    'h0' : 0.5961
}

params = {
    'ie' : 0,
    'is_Ie_time_dep' :  False,
    'is_Ie_sinusoidal' : False,
    'current_pulse_length' : 0,
    'c_m' : 1
}

n, m, h, i_k, i_na, i_leak, v_1a, t = euler(hodgkin_huxley_model, t_max, dt, params, initial_values);
```

In [21]:
```python
fig = plt.gcf()
ax.ticklabel_format(useOffset=False)

plt.title('Membrane Voltage Over Time')
plt.plot(t,v_1a)
plt.xlabel('t (ms)')
plt.ylabel('V (mV)');
```

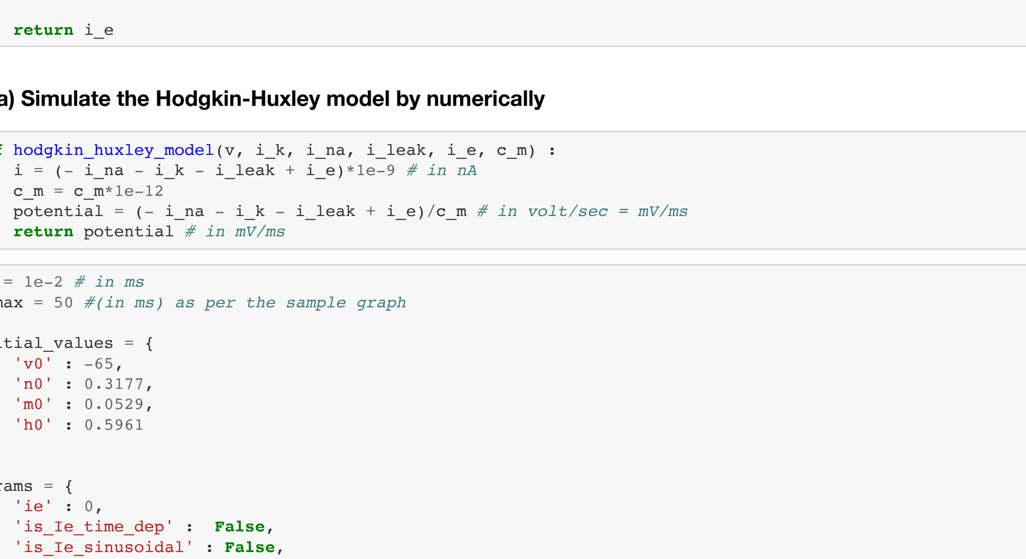


Discussion: A damped oscillation with a very small amplitude is visible as expected.

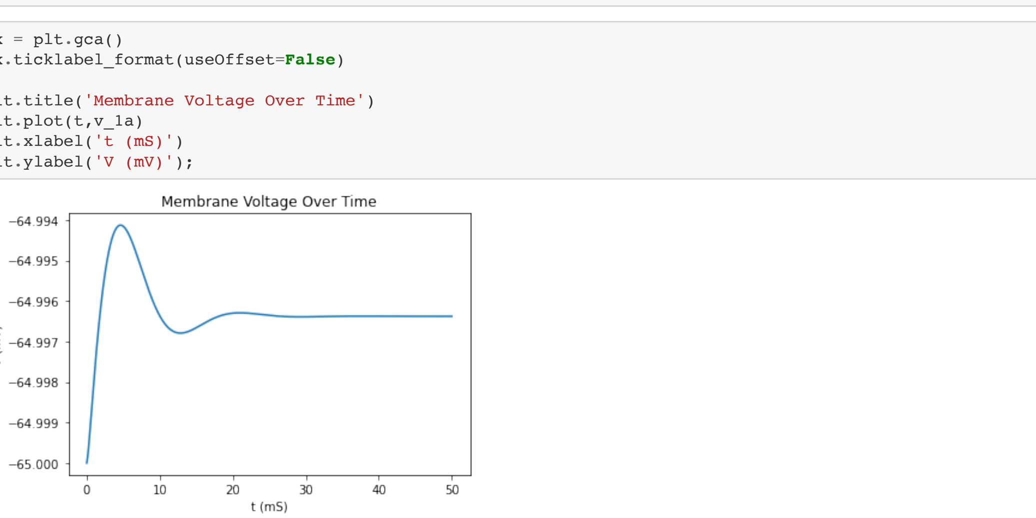
2 (b) Apply now a constant external current Ie = 20 pA

In [22]:
```python
params['ie'] = 20*1e-12

n, m, h, i_k, i_na, i_leak, v_1b, t = euler(hodgkin_huxley_model, t_max, dt, params, initial_values)
```

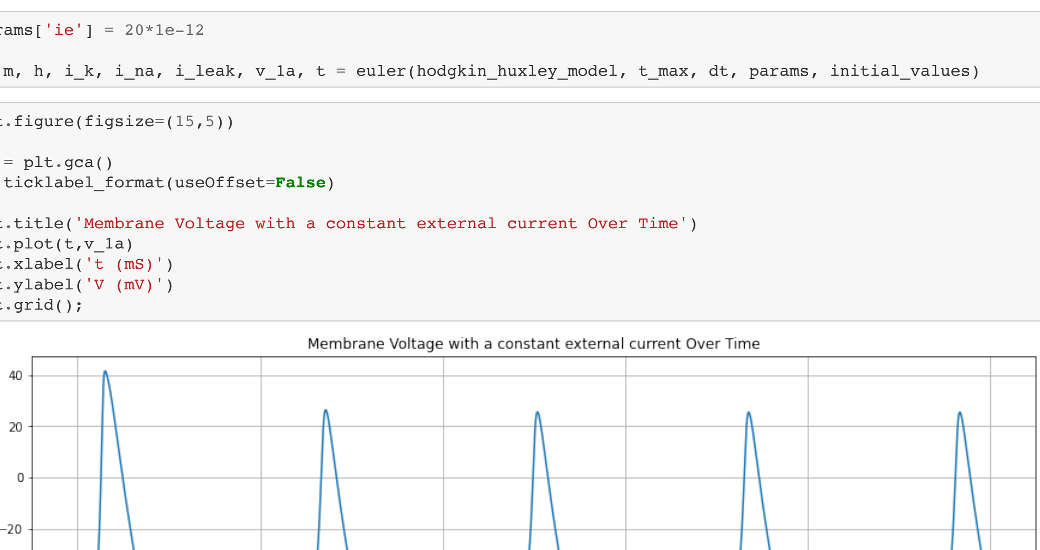
In [23]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Membrane Voltage with a constant external current Over Time')
plt.plot(t,v_1b)
plt.xlabel('t (ms)')
plt.ylabel('V (mV)')
plt.grid()
```



In [24]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Potassium and Sodium Currents with a constant external current Over Time')
plt.plot(t, i_k, label='Potassium Current')
plt.plot(t, -i_na, label='Negative Sodium Current')
plt.xlabel('t (ms)')
plt.ylabel('Current (A)')
plt.legend();
```



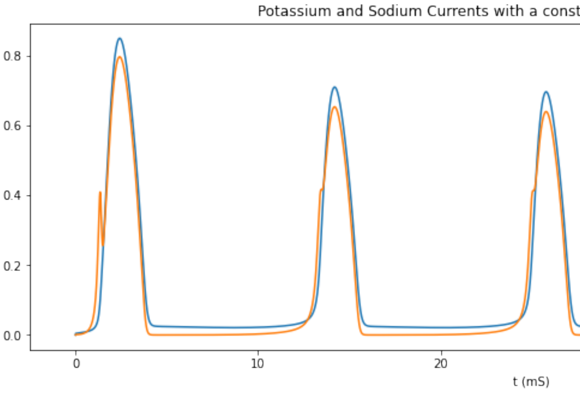
In [25]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Potassium and Sodium Currents with a constant external current Over Time')
plt.plot(t, n, label='potassium gate opening probability(n)')
plt.plot(t, m, label='Sodium gate opening probability(m)')
plt.plot(t, h, label='Sodium gate closing probability(h)')
plt.xlabel('t (ms)')
plt.ylabel('Probability')
plt.legend();
```



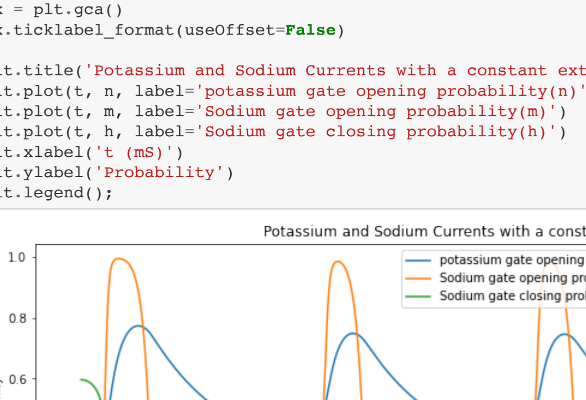
Discussion:

- With an external current the membrane voltage increases to reach above the threshold voltage
- The Sodium gate opening probability increases rapidly and closing probability decreases slowly, resulting in the rapid increase in Sodium current (current flowing inside the neuron) resulting in **Depolarization**. Along with this the Potassium gate probability increases very slowly.
- When the voltage reaches the maximum voltage that results in sudden decrease of the Sodium opening probability and increase in Sodium gate closing probability. At the same time, the potassium gate probability increases. Resulting in **Repolarization**.
- The Potassium gate takes a longer time to close thus resulting in a **Hyperpolarization**
- The slow opening of the sodium gate then slowly moves back the membrane voltage to rest

In [26]:
```python
plt.title('Potassium gating variable (n) as a function of the voltage')
plt.plot(v_1b, n)
plt.xlabel('V (mV)')
plt.ylabel('Probability(n)');
```



In [27]:
```python
plt.title('Potassium current I_k as a function of the voltage')
plt.plot(v_1b, i_k)
plt.xlabel('V (mV)')
plt.ylabel('Potassium current(A)');
```



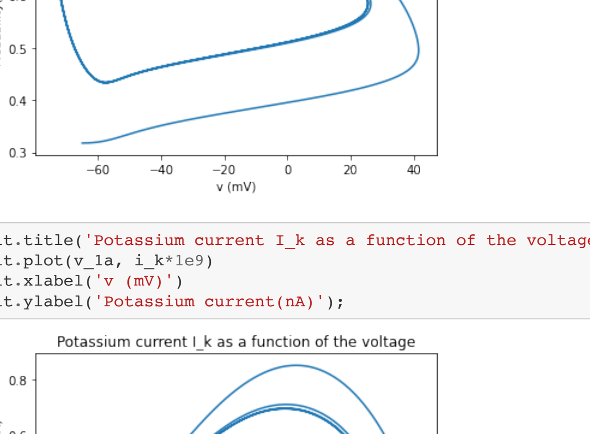
Discussion: Initially, the higher shape proves that the potassium probability and current increases. But when it reaches the maximum voltage, the probability and current values increases and goes in a loop as the voltage again decreases back. The hyperpolarization impact are also clearly visible.

1 (c) Plot the firing rate of the model as a function of Ie over the range from 0 to 20 pA.

In [28]:
```python
def get_firing_rate(v, dt):
    spike_indices = np.zeros(0)
    v_thresh = -54 # mV
    spike_count = 0
    for i in range(len(v)-1):
        if(v[i] < v_thresh and v[i+1] >= v_thresh):
            spike_indices = np.append(spike_indices, i)
            spike_count += 1

    if spike_count < 2:
        return 0
    #
    #
    #
    else:
        isi = (spike_indices[1] - spike_indices[0])*dt
        return 1/isi
```

In [29]:
```python
i_e_range = np.arange(0, 21, 1) # in pA
firing_rates = np.zeros(len(i_e_range))
# ...

for i in range(len(i_e_range)):
    params['ie'] = i_e_range[i]*1e-12
    _, _, _, _, _, _, v, _ = euler(hodgkin_huxley_model, t_max, dt, params, initial_values)
    firing_rates[i] = get_firing_rate(v, dt)

plt.title('Firing Rate as a function of the voltage')
plt.plot(i_e_range, firing_rates)
plt.xlabel('Ie (in pA)')
plt.ylabel('Firing Rate (Hz)');

print(f'{max(firing_rates) = }')
```

```
max(firing_rates) = 84.58608058608059
```



Discussion:

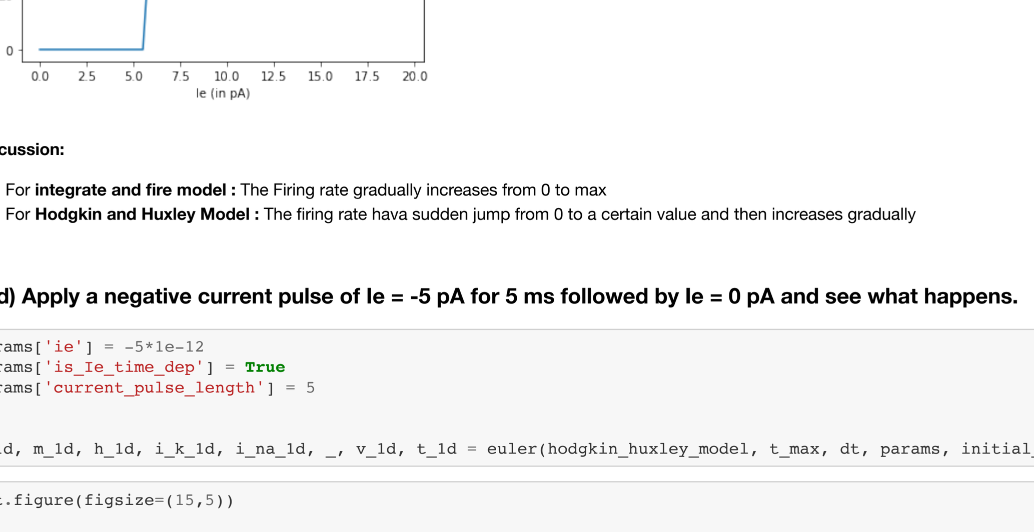
- For **integrate and fire model** : The Firing rate gradually increases from 0 to max.
- For **Hodgkin and Huxley Model** : The firing rate have sudden jump from 0 to a certain value and then increases gradually

1 (d) Apply a negative current pulse of Ie = -5 pA for 5 ms followed by Ie = 0 pA and see what happens.

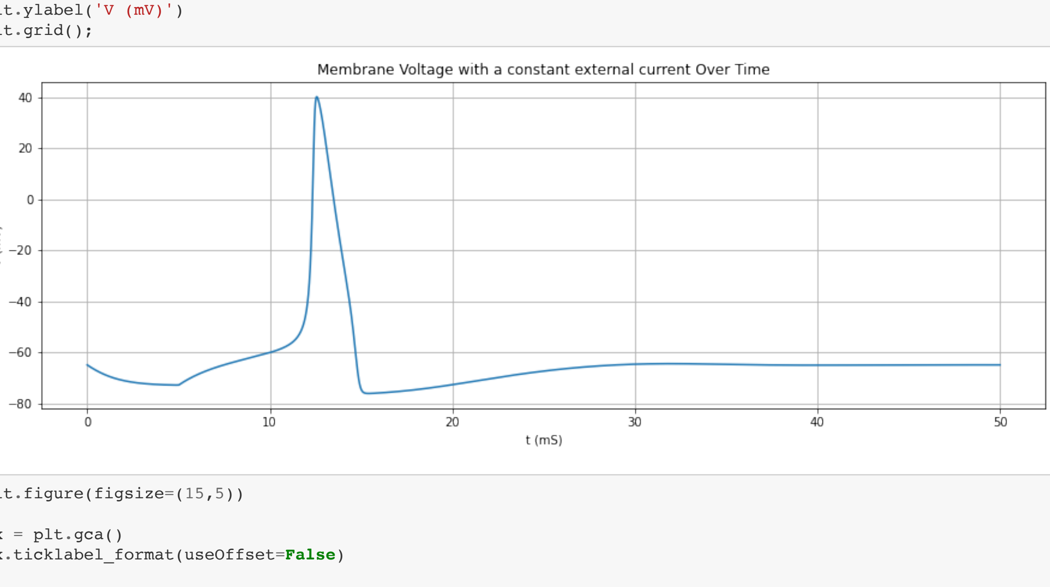
In [30]:
```python
params['ie'] = -5*1e-12
params['is_Ie_time_dep'] = True
params['current_pulse_length'] = 5

n_1d, m_1d, h_1d, i_k_1d, i_na_1d, i_leak_1d, v_1d, t_1d = euler(hodgkin_huxley_model, t_max, dt, params, initial_values)
```

In [31]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Membrane Voltage with a constant external current Over Time')
plt.plot(t_1d,v_1d)
plt.xlabel('t (ms)')
plt.ylabel('V (mV)')
plt.grid()
```

In [32]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Potassium and Sodium Currents with a constant external current Over Time')
plt.plot(t_1d, i_k_1d, label='Potassium Current')
plt.plot(t_1d, -i_na_1d, label='Negative Sodium Current')
plt.xlabel('t (ms)')
plt.ylabel('Current (A)')
plt.legend();
```



In [33]:
```python
plt.figure(figsize=(15,5))

ax = plt.gca()
ax.ticklabel_format(useOffset=False)

plt.title('Potassium and Sodium Currents with a constant external current Over Time')
plt.plot(t_1d, n_1d, label='potassium gate opening probability(n)')
plt.plot(t_1d, m_1d, label='Sodium gate opening probability(m)')
plt.plot(t_1d, h_1d, label='Sodium gate closing probability(h)')
plt.xlabel('t (ms)')
plt.ylabel('Probability')
plt.legend();
```



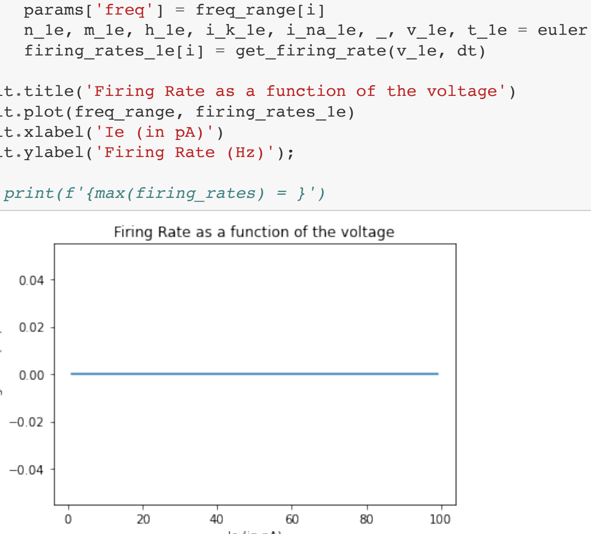
Discussion :

- Even if the external current is negative, due to sudden change in current the voltage increases resulting in an action potential

1 (e) (bonus) Drive your Hodgkin-Huxley neuron with an external sinusoidal current $Ie = I0 \sin(2\pi f t)$ with $I0 = 2$ pA.

In [34]:
```python
def get_time_max(freq, dt, no_of_osc):
    time_prd_1_osc = 1/freq
#   ...
#   ...
    t_max = ...
    return t_max
```

In [35]:
```python
params['is_Ie_time_dep'] = False
params['is_Ie_sinusoidal'] = True

freq_range = np.arange(1, 100, 10)
firing_rates = np.zeros(len(freq_range))

for i in range(len(freq_range)):
    t_max = get_time_max(freq_range[i], dt, 20)
    params['freq'] = freq_range[i]
    _, _, _, _, _, _, v, _ = euler(hodgkin_huxley_model, t_max, dt, params, initial_values)
    firing_rates[i] = get_firing_rate(v, dt)

plt.title('Firing Rate as a function of this voltage')
plt.plot(freq_range, firing_rates)
plt.xlabel('f (in Hz)')
plt.ylabel('Firing Rate (Hz)');

# print(f'{max(firing_rates) = }')
```



In [ ]: