

waiting-time-distributions

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1 Waiting time distributions

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Many stochastic processes can be characterized by the life time of the states that a given system can be found in. By monitoring the waiting times one can obtain so called waiting time distributions, which often are a good indicator for the underlying physical/stochastic process. The analysis of waiting time distributions is also useful to address the question if a given system has internal (hidden) substates, which might reveal their existence by modulating the observed waiting time distribution. Often one does not know a priori how many internal states there are, and one might find an answer to this question by investigating the waiting time distributions.

1.2 A simple one-step process

For a very simple example, we start by considering a state with a characteristic mean life time τ . It is well known, that the waiting time distribution then is a simple exponential distribution

$$p(t) = \frac{1}{\tau} \exp(-t / \tau). \quad (1)$$

Note that this is exactly an exponential distribution with mean $\lambda = 1/\tau$

$$f_\lambda(x) = \lambda \exp(-\lambda x) \quad \text{for } x > 0, \quad (2)$$

where f_λ is the PDF of the exponential distribution, which has a mean value

$$\langle x \rangle = \frac{1}{\lambda}. \quad (3)$$

The exponential distribution is the generic waiting time distribution for a stochastic process with a mean waiting time

$$\langle t \rangle = \tau. \quad (4)$$

This can of course also (self-consistently) expressed by rephrasing, that

$$\langle t \rangle = \int_0^\infty t \cdot p(t) dt \quad (5)$$

holds. If you are interested in this integral, recall that

$$\int x \exp(-ax) dx = -\frac{1}{a^2} (1 + ax) \exp(-ax) \quad (6)$$

such that

$$\int_0^\infty t \cdot \frac{1}{\tau} \exp(-t / \tau) dt = \frac{1}{\tau} [-\tau^2(1 + t / \tau) \exp(-t / \tau)]_0^\infty = \frac{1}{\tau} (\tau^2(1 + 0) \cdot 1) = \tau, \quad (7)$$

as expected.

1.3 A generic (sequential two-step process)

Now we consider a sequential two-step process, where a first step A is always followed by a second step B , with characteristic time scales τ_A and τ_B , respectively. Their individual waiting time distributions are of course again exponential distributions

$$p_A(t) = \frac{1}{\tau_A} \exp(-t / \tau_A) \quad (8)$$

$$p_B(t) = \frac{1}{\tau_B} \exp(-t / \tau_B). \quad (9)$$

The observed waiting time distribution for such a two step process, where we only can monitor the time t after both steps have been carried out, is given by a convolution integral of both processes

$$p(t) = \int_0^t p_A(\tau) p_B(t - \tau) d\tau \quad (10)$$

$$= \frac{1}{\tau_A \tau_B} \int_0^t \exp(-\tau / \tau_A) \exp(-(t - \tau) / \tau_B) d\tau \quad (11)$$

$$= \frac{1}{\tau_A \tau_B} \int_0^t \exp\left(\frac{-\tau_B \tau - \tau_A t + \tau_A \tau}{\tau_A \tau_B}\right) d\tau \quad (12)$$

$$= \frac{\exp(-\tau_A t / \tau_A \tau_B)}{\tau_A \tau_B} \int_0^t \exp\left(\frac{-(\tau_B - \tau_A) \tau}{\tau_A \tau_B}\right) d\tau \quad (13)$$

$$= \frac{\exp(-\tau_A t / \tau_A \tau_B)}{\tau_A \tau_B} \left[\frac{-\tau_A \tau_B}{\tau_B - \tau_A} \exp\left(\frac{-(\tau_B - \tau_A) \tau}{\tau_A \tau_B}\right) \right]_0^t \quad (14)$$

$$= \frac{\exp(-\tau_A t / \tau_A \tau_B)}{\tau_B - \tau_A} \left(-\exp(-(\tau_B - \tau_A) t / \tau_A \tau_B) + 1 \right) \quad (15)$$

$$= \frac{1}{\tau_B - \tau_A} \left(\exp(-t / \tau_B) - \exp(-t / \tau_A) \right) \quad (16)$$

Remember, that we always assume, that the two processes happen in the same sequential order (first A , followed by step B). Below we show by direct numerical sampling, that this is indeed the case and compare the observed waiting time distributions for the one and two step process.

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

```
In [2]: def getHistogramCoordinates(X, nbins, normed = True):
'''
Creates x,y data pairs of the histogram data using
numpy's histogram function.
'''
```

```

hist, bin_edges = np.histogram(X, bins = nBins, normed = True)
bin_centers = (bin_edges[1:] + bin_edges[0:-1]) / 2.0
assert hist.shape == bin_centers.shape, "Error: Shape assertion failed."

res = np.zeros((nBins, 2))
res[:, 0] = bin_centers
res[:, 1] = hist
return res

In [3]: %matplotlib inline
        %config InlineBackend.figure_formats = {'png', 'retina'}

In [4]: # this is how we can use python to sample from an exponential distribution
        # with a given mean value (here meanTime)
        meanTime = 1.5
        sampleTime = np.random.exponential(meanTime)
        print("sample waiting time =", sampleTime)

sample waiting time = 0.5172097936192911

In [5]: # specify the number of samples
        nSamples = 5000
        meanTime = 1.5
        sampleTimes = np.random.exponential(meanTime, nSamples)

        assert sampleTimes.shape == (nSamples,), "Error: Shape assertion failed."
        print(sampleTimes.shape)

(5000,)

```

Next we create the theoretical distribution, which for this case is of course the standard probability density function of the exponential distribution.

```

In [6]: # create the theoretical exponential distribution
        nVisPoints = 500
        meanValue = meanTime
        xVals = np.linspace(0.0, 20.0, nVisPoints)
        yVals = np.array([np.exp(-t / meanValue) / meanValue for t in xVals])
        expDist = np.zeros((nVisPoints, 2))
        expDist[:, 0] = xVals
        expDist[:, 1] = yVals

In [7]: # plotting function to plot the numerically sampled data
        # in conjunction with the exponential distribution

def plot_histogram_wDist(X, nBins, dist):

```

```

fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

ax.hist(X,
        bins = nBins,
        density = True,
        label = r'sampled')

ax.plot(dist[:, 0], dist[:, 1],
        lw = 1.5,
        color = 'C3',
        label = r'$\mathrm{Exp}(\lambda = \langle t \rangle)$')

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 15.1, 2.0)
minor_x_ticks = np.arange(0.0, 15.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0
for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

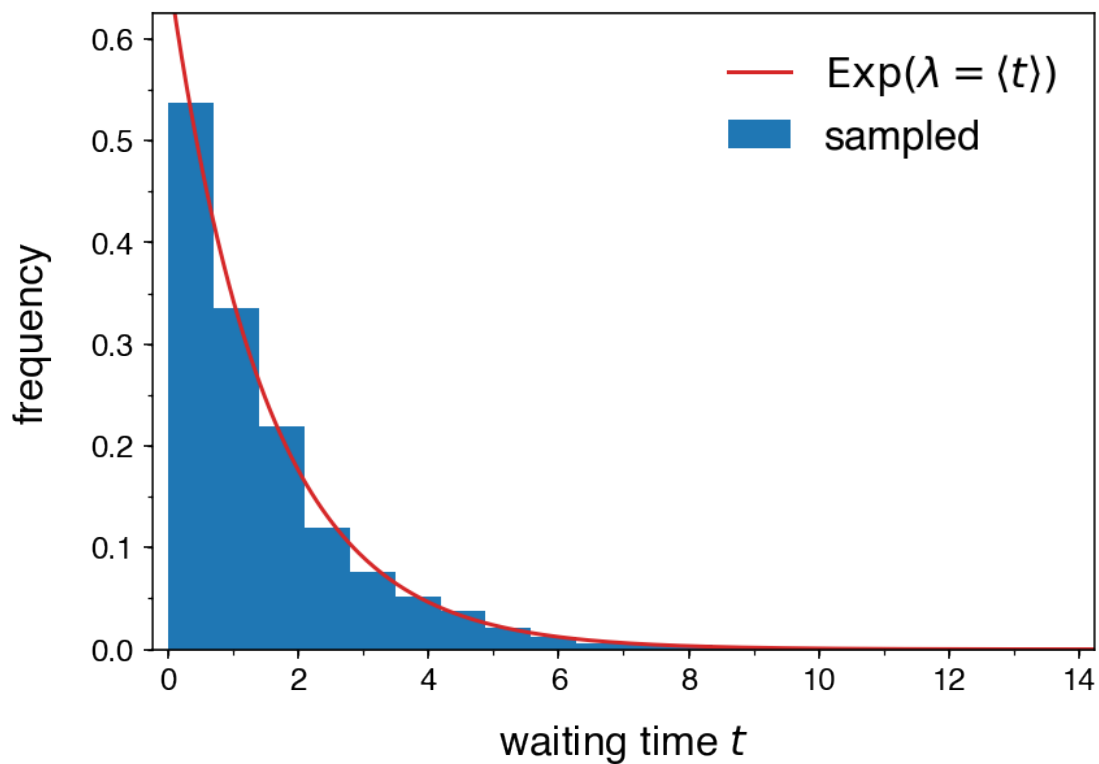
ax.set_xlim(-0.25, 14.25)
ax.set_ylim(0.0, 0.625)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
                # loc = 'upper left',
                fontsize = 16.0,
                handlelength = 1.5,
                scatterpoints = 1,
                markerscale = 1.0,
                ncol = 1)
leg.draw_frame(False)

return None

```

```
In [8]: nBins = 20
        plot_histogram_wDist(sampleTimes, nBins, expDist)
```



```
In [9]: # plotting function to show that both version of the histogram
        # of course perfectly overlay each other
```

```
def plot_histogram_comparison(X, nBins, scatterData, dist):

    fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

    ax.hist(X,
            bins = nBins,
            density = True,
            label = r'sampled',
            zorder = 1)

    ax.plot(dist[:, 0], dist[:, 1],
            lw = 1.5,
            color = 'C3',
            label = r'$\mathrm{Exp}(\lambda = \langle t \rangle)$',
            zorder = 3)
```

```

ax.scatter(scatterData[:, 0], scatterData[:, 1],
           s = 50,
           lw = 1.5,
           facecolor = 'None',
           edgecolor = 'C3',
           zorder = 2)

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 15.1, 2.0)
minor_x_ticks = np.arange(0.0, 15.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0
for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

ax.set_xlim(-0.25, 14.25)
ax.set_ylim(0.0, 0.625)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
                # loc = 'upper left',
                fontsize = 16.0,
                handlelength = 1.5,
                scatterpoints = 1,
                markerscale = 1.0,
                ncol = 1)
leg.draw_frame(False)

return None

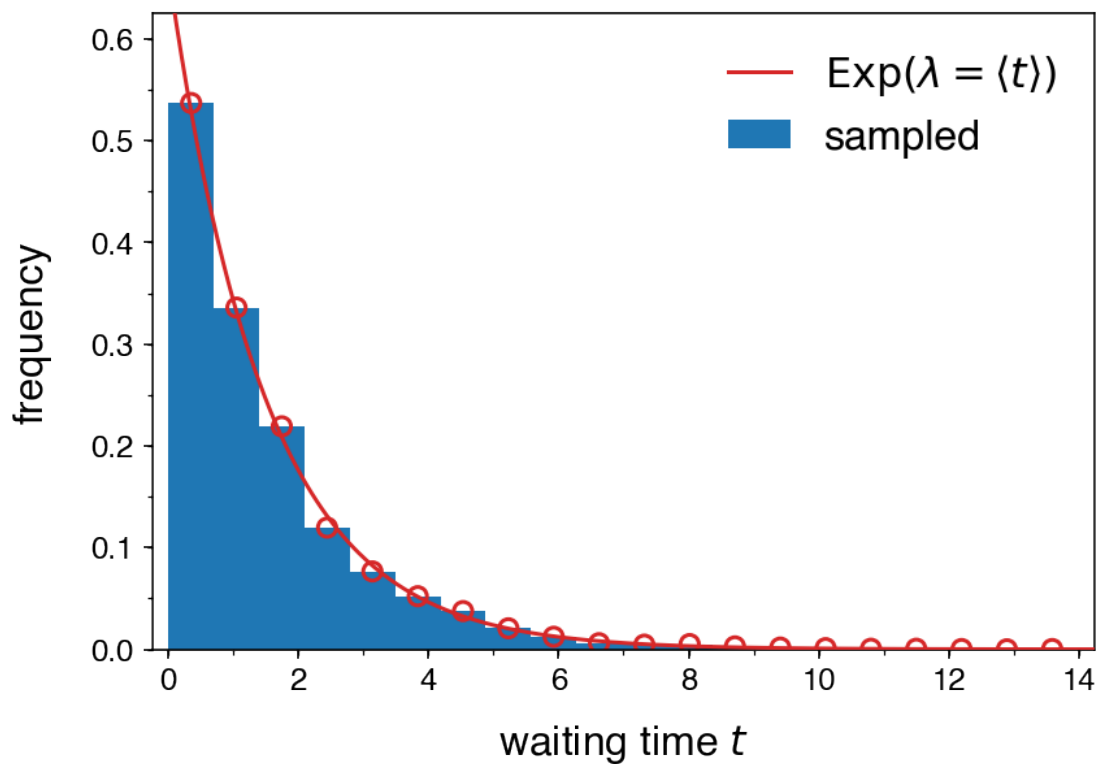
```

```

In [10]: # for an alternative histogram representation I
# create x,y data pairs of the histogram data using
# numpy's histogram function
nBins = 20
scatterData = getHistogramCoordinates(sampleTimes, nBins, normed = True)

```

```
plot_histogram_comparison(sampleTimes, nBins, scatterData, expDist)
```



```
In [11]: def plot_scatter_histogram(X, dist):

    fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

    ax.plot([-1.0, 20.0], [0.0, 0.0],
            dashes = [6.0, 3.0],
            color = '#CCCCCC',
            lw = 1.0,
            zorder = 1)

    ax.plot(dist[:, 0], dist[:, 1],
            lw = 1.5,
            color = 'C3',
            label = r'$\mathrm{Exp}(\lambda = \langle t \rangle)$',
            zorder = 3)

    ax.scatter(X[:, 0], X[:, 1],
              s = 50,
              lw = 1.5,
```

```

        facecolor = 'None',
        edgecolor = 'C3',
        zorder = 2,
        label = r'sampled')

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 15.1, 2.0)
minor_x_ticks = np.arange(0.0, 15.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0
for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

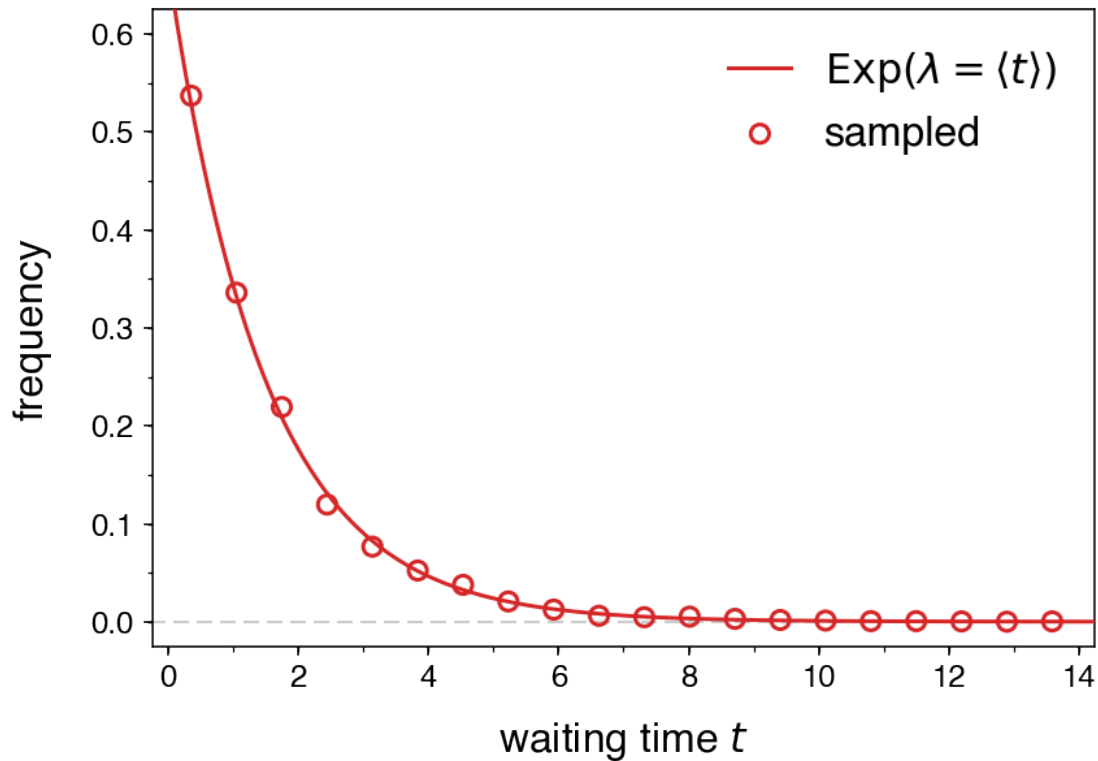
ax.set_xlim(-0.25, 14.25)
ax.set_ylim(-0.025, 0.625)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
                # loc = 'upper left',
                fontsize = 16.0,
                handlelength = 1.5,
                scatterpoints = 1,
                markerscale = 1.0,
                ncol = 1)
leg.draw_frame(False)

return None

```

In [12]: plot_scatter_histogram(scatterData, expDist)



Next we consider a two-step process. The first process has a mean waiting time τ_A and the second process a mean waiting time τ_B .

```
In [13]: # set the mean waiting times for the two-step process
tau_A = 1.0
tau_B = 1.5

# specify the number of samples
nSamples = 500000

tauAs = np.random.exponential(tau_A, nSamples)
tauBs = np.random.exponential(tau_B, nSamples)
assert tauAs.shape == tauBs.shape

observedTimes = tauAs + tauBs # a sequential two step process
assert observedTimes.shape == (nSamples,), "Error: Shape assertion failed."
print(observedTimes.shape)
```

(500000,)

```
In [14]: # create the theoretical distribution
# Here this distribution is the convolution of two exponential distributions.
```

```

nVisPoints = 300
tau_A = 1.0
tau_B = 1.5
xVals = np.linspace(-2.0, 20.0, nVisPoints)
yVals = np.array([(np.exp(-t / tau_B) - np.exp(-t / tau_A)) \
                  / (tau_B - tau_A) for t in xVals])
dist2 = np.zeros((nVisPoints, 2))
dist2[:, 0] = xVals
dist2[:, 1] = yVals

```

In [15]: *# plotting function to plot the numerically sampled data
in conjunction with the exponential distribution*

```

def plot_histogram_wDist_2step(X, nBins, dist):

    fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

    ax.hist(X,
            bins = nBins,
            density = True,
            label = r'sampled')

    ax.plot(dist[:, 0], dist[:, 1],
            lw = 1.5,
            color = 'C3',
            label = r'$p(t)$')

    ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
    ax.set_ylabel(r'frequency', fontsize = 16.0)
    ax.xaxis.labelpad = 10.0
    ax.yaxis.labelpad = 15.0

    major_x_ticks = np.arange(0.0, 15.1, 2.0)
    minor_x_ticks = np.arange(0.0, 15.1, 1.0)
    ax.set_xticks(major_x_ticks)
    ax.set_xticks(minor_x_ticks, minor = True)

    major_y_ticks = np.arange(0.0, 1.1, 0.1)
    minor_y_ticks = np.arange(0.0, 1.1, 0.05)
    ax.set_yticks(major_y_ticks)
    ax.set_yticks(minor_y_ticks, minor = True)

    labelfontsize = 12.0
    for tick in ax.xaxis.get_major_ticks():
        tick.label.set_fontsize(labelfontsize)
    for tick in ax.yaxis.get_major_ticks():
        tick.label.set_fontsize(labelfontsize)

```

```

ax.set_xlim(-0.25, 15.75)
ax.set_ylim(0.0, 0.315)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
               # loc = 'upper left',
               fontsize = 16.0,
               handlelength = 1.5,
               scatterpoints = 1,
               markerscale = 1.0,
               ncol = 1)
leg.draw_frame(False)

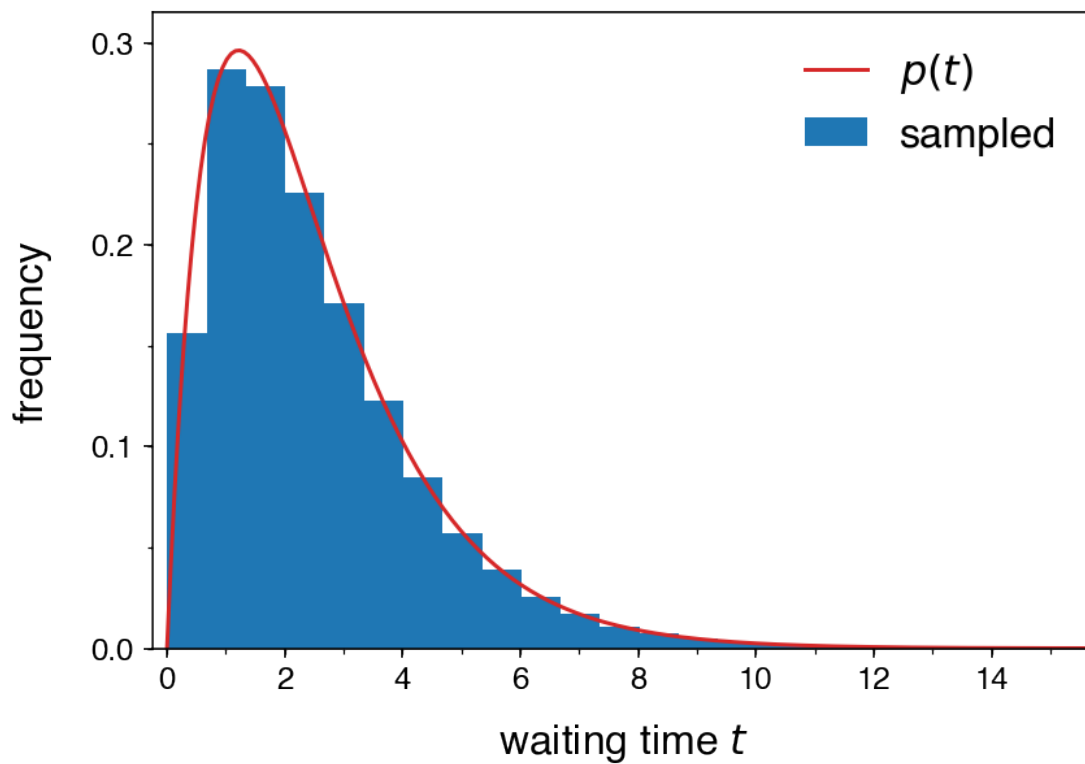
return None

```

```

In [16]: nBins = 30
         plot_histogram_wDist_2step(observedTimes, nBins, dist2)

```



```

In [17]: def plot_scatter_histogram(X, dist):

         fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

```

```

ax.plot([-1.0, 20.0], [0.0, 0.0],
        dashes = [6.0, 3.0],
        color = '#CCCCCC',
        lw = 1.0,
        zorder = 1)

ax.plot(dist[:, 0], dist[:, 1],
        lw = 1.5,
        color = 'C3',
        label = r'$p(t)$',
        zorder = 3)

ax.scatter(X[:, 0], X[:, 1],
           s = 50,
           lw = 1.5,
           facecolor = 'None',
           edgecolor = 'C3',
           zorder = 2,
           label = r'sampled')

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 15.1, 2.0)
minor_x_ticks = np.arange(0.0, 15.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0
for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

ax.set_xlim(-0.25, 15.75)
ax.set_ylim(-0.025, 0.315)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
                # loc = 'upper left',
                fontsize = 16.0,

```

```

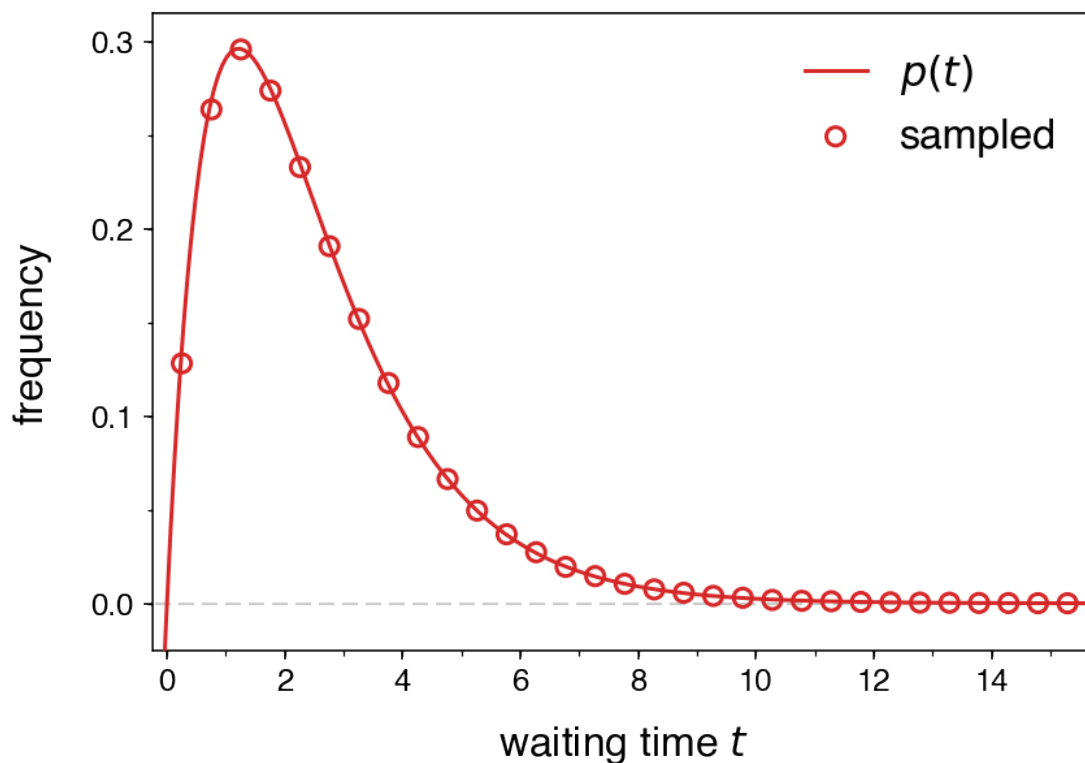
        handlelength = 1.5,
        scatterpoints = 1,
        markerscale = 1.0,
        ncol = 1)
    leg.draw_frame(False)

    return None

In [18]: # for an alternative histogram representation I
# create x,y data pairs of the histogram data using
# numpy's histogram function
nBins = 40
scatterData2 = getHistogramCoordinates(observedTimes, nBins, True)

plot_scatter_histogram(scatterData2, dist2)

```



```

In [19]: def plot_one_vs_two(X1, dist1, X2, dist2):

    fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

    ax.plot([-1.0, 20.0], [0.0, 0.0],
            dashes = [6.0, 3.0],

```

```

        color = '#CCCCCC',
        lw = 1.0,
        zorder = 1)

ax.plot(dist1[:, 0], dist1[:, 1],
        lw = 1.5,
        color = 'C0',
        label = r'$p(t)$',
        zorder = 3)

ax.plot(dist2[:, 0], dist2[:, 1],
        lw = 1.5,
        color = 'C3',
        label = r'$p(t)$',
        zorder = 3)

ax.scatter(X1[:, 0], X1[:, 1],
          s = 50,
          lw = 1.5,
          facecolor = 'None',
          edgecolor = 'C0',
          zorder = 2,
          label = r'one step (sampled)')

ax.scatter(X2[:, 0], X2[:, 1],
          s = 50,
          lw = 1.5,
          facecolor = 'None',
          edgecolor = 'C3',
          zorder = 2,
          label = r'two step (sampled)')

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'$p(t)$ observed / frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 15.1, 2.0)
minor_x_ticks = np.arange(0.0, 15.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0

```

```

for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

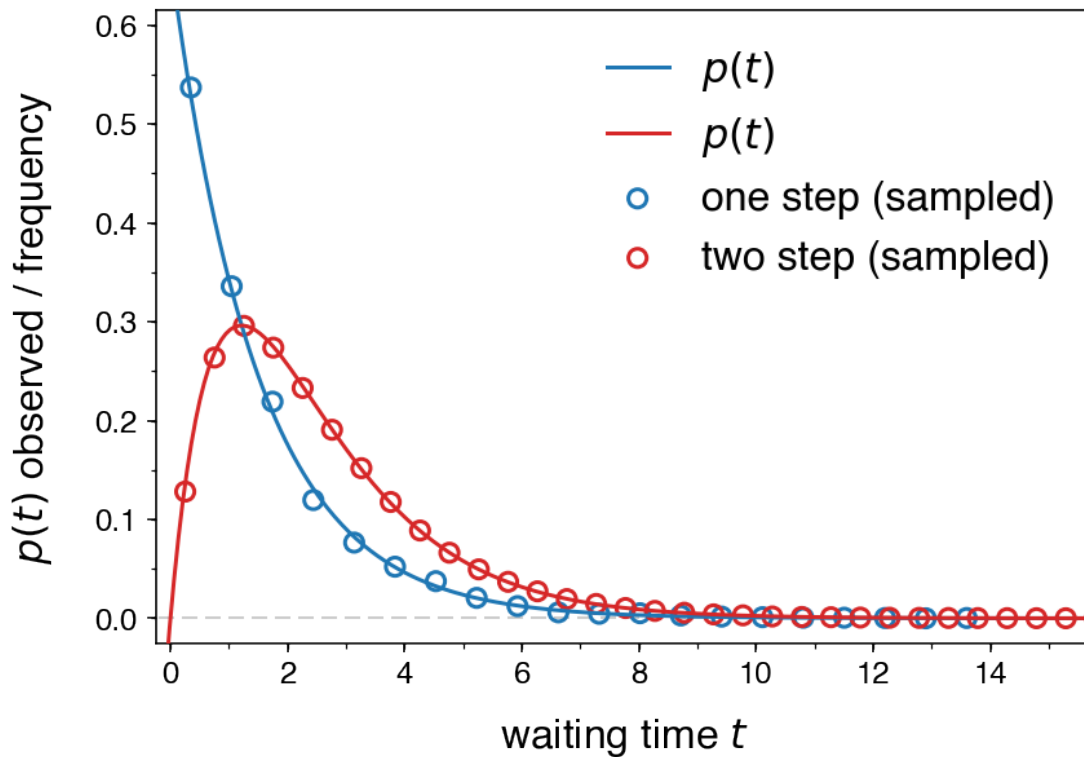
ax.set_xlim(-0.25, 15.75)
ax.set_ylim(-0.025, 0.615)
ax.set_axisbelow(False)

leg = ax.legend(# bbox_to_anchor = [1.0, 1.0],
               # loc = 'upper left',
               fontsize = 16.0,
               handlelength = 1.5,
               scatterpoints = 1,
               markerscale = 1.0,
               ncol = 1)
leg.draw_frame(False)

return None

```

In [20]: `plot_one_vs_two(scatterData, expDist, scatterData2, dist2)`



In the plot above, we see that the observed waiting time distribution $p(t)$ of a one-step process is fundamentally different from the observed waiting time distribution of a two-step process (1

hidden internal state). This internal state can thus be revealed by analysis of waiting time distributions.

1.4 Multi-step processes with equal characteristic time

Below we consider a multistep process, where each individual process has the same identical characteristic mean waiting time τ .

```
In [21]: # set the mean waiting times for a multi-step process
        tau = 1.0
        nBins = 50

        # specify the number of samples
        nSamples = 500000
        steps_list = [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]

        res = []
        for j, steps in enumerate(steps_list):

            observedTimes = np.zeros((nSamples))

            for i in range(steps):

                observedTimes += np.random.exponential(tau, nSamples)

            assert observedTimes.shape == (nSamples,), "Error: Shape assertion failed."

            tmp = getHistogramCoordinates(observedTimes, nBins, True)
            res.append(tmp)

In [22]: def plot_multi(res, labels):

        assert len(res) == len(labels), "Error: Length assertion failed."

        fig, ax = plt.subplots(1, 1, figsize = (6.5, 4.5))

        ax.plot([-1.0, 20.0], [0.0, 0.0],
                dashes = [6.0, 3.0],
                color = '#CCCCCC',
                lw = 1.0,
                zorder = 1)

        for i in range(len(res)):

            X = res[i]

            ax.plot(X[:, 0], X[:, 1],
                    lw = 1.5,
```



```

        # color = 'C0',
        label = labels[i],
        zorder = 3)

ax.set_xlabel(r'waiting time $t$', fontsize = 16.0)
ax.set_ylabel(r'$p(t)$ observed / frequency', fontsize = 16.0)
ax.xaxis.labelpad = 10.0
ax.yaxis.labelpad = 15.0

major_x_ticks = np.arange(0.0, 20.1, 2.0)
minor_x_ticks = np.arange(0.0, 20.1, 1.0)
ax.set_xticks(major_x_ticks)
ax.set_xticks(minor_x_ticks, minor = True)

major_y_ticks = np.arange(0.0, 1.1, 0.1)
minor_y_ticks = np.arange(0.0, 1.1, 0.05)
ax.set_yticks(major_y_ticks)
ax.set_yticks(minor_y_ticks, minor = True)

labelfontsize = 12.0
for tick in ax.xaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)
for tick in ax.yaxis.get_major_ticks():
    tick.label.set_fontsize(labelfontsize)

ax.set_xlim(-0.25, 20.25)
ax.set_ylim(-0.025, 0.615)
ax.set_axisbelow(False)

leg = ax.legend(bbox_to_anchor = [1.0, 1.0],
                loc = 'upper left',
                fontsize = 16.0,
                handlelength = 1.5,
                scatterpoints = 1,
                markerscale = 1.0,
                ncol = 1)
leg.draw_frame(False)

return None

```

In [23]: *# plot the mult-step results*

```

labels = [r'$n = 1$',
          r'$n = 2$',
          r'$n = 3$',
          r'$n = 4$',
          r'$n = 5$',

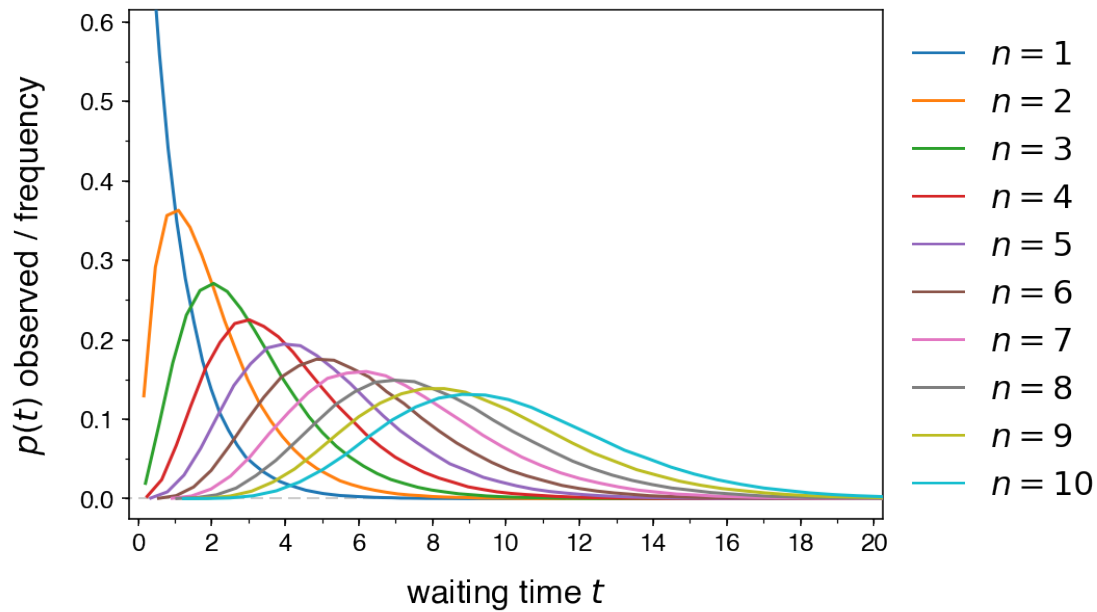
```

```

r['$n = 6$'],
r['$n = 7$'],
r['$n = 8$'],
r['$n = 9$'],
r['$n = 10$']

```

```
plot_multi(res, labels)
```



For further information on this topic, have a look at the following two sources:

- Rob Phillips et al. - **Physical Biology of the Cell** (2nd edition, 2013). They discuss this issue in the context of molecular motors, where multiple internal states of a molecular motor are often hidden, i.e. not accessible to direct experimental observation. However sometimes one can reveal the existence of such states by analyzing the corresponding waiting-time distributions.
- D. L. Floyd et al. - Analysis of Kinetic Intermediates in Single-Particle Dwell-Time Distributions, *Biophysical Journal*, **99**, 360-366, 2010.