4.1.2 Markov State Models

- This module will consist of
  - an explanation of Markov State Models in the analysis of biological MD
  - a tutorial on pyemma
- At the end of this module, you should be able to
  - answer the following questions:
    - what is a transition matrix and why is it useful?
    - what is a MSM?
  - build a MSM using pyemma

Molecular simulations as Markov chains

- Molecular simulations can be thought of as Markov chains - where the future is only dependent on the present, not the past
  - Always true for MCMC
  - After a sufficient amount of lag time, true for molecular dynamics
- A Markov chain is a *single realization* of a Markov process

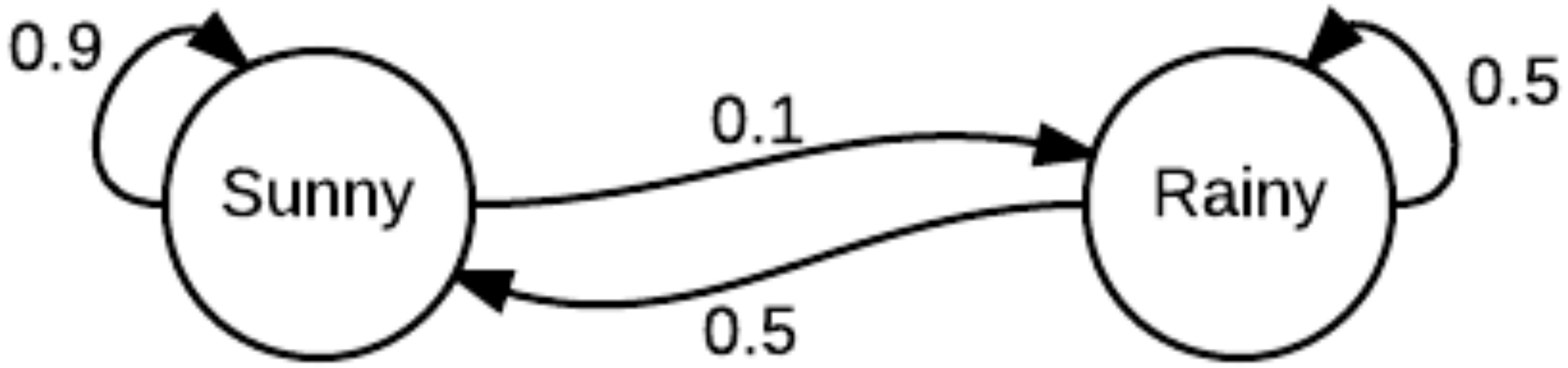
Transition Matrices

- The *complete description* of the dynamics of a Markov system is contained in a transition matrix.
- If the probability of moving from i to j in one time step is $Pr(j \mid i) = P_{i,j}$, the transition matrix P is given by,

$$P = \begin{bmatrix} P_{1,1} & P_{1,2} & \dots & P_{1,j} & \dots & P_{1,S} \\ P_{2,1} & P_{2,2} & \dots & P_{2,j} & \dots & P_{2,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{i,1} & P_{i,2} & \dots & P_{i,j} & \dots & P_{i,S} \\ \vdots & \vdots & \ddots & \vdots & \ddots & \vdots \\ P_{S,1} & P_{S,2} & \dots & P_{S,j} & \dots & P_{S,S} \end{bmatrix}.$$

Exercise: Transition Matrices

- Suppose that weather is a Markov process and it is either sunny or rainy.



- Given these transition probabilities, write a transition matrix for the process. Remember that the probability of moving from i to j in one time step is $Pr(j \mid i) = P_{i,j}$.

$$\begin{bmatrix} 0.9 & 0.1 \\ 0.5 & 0.5 \end{bmatrix}$$

Exercise: Transition Matrix Powers

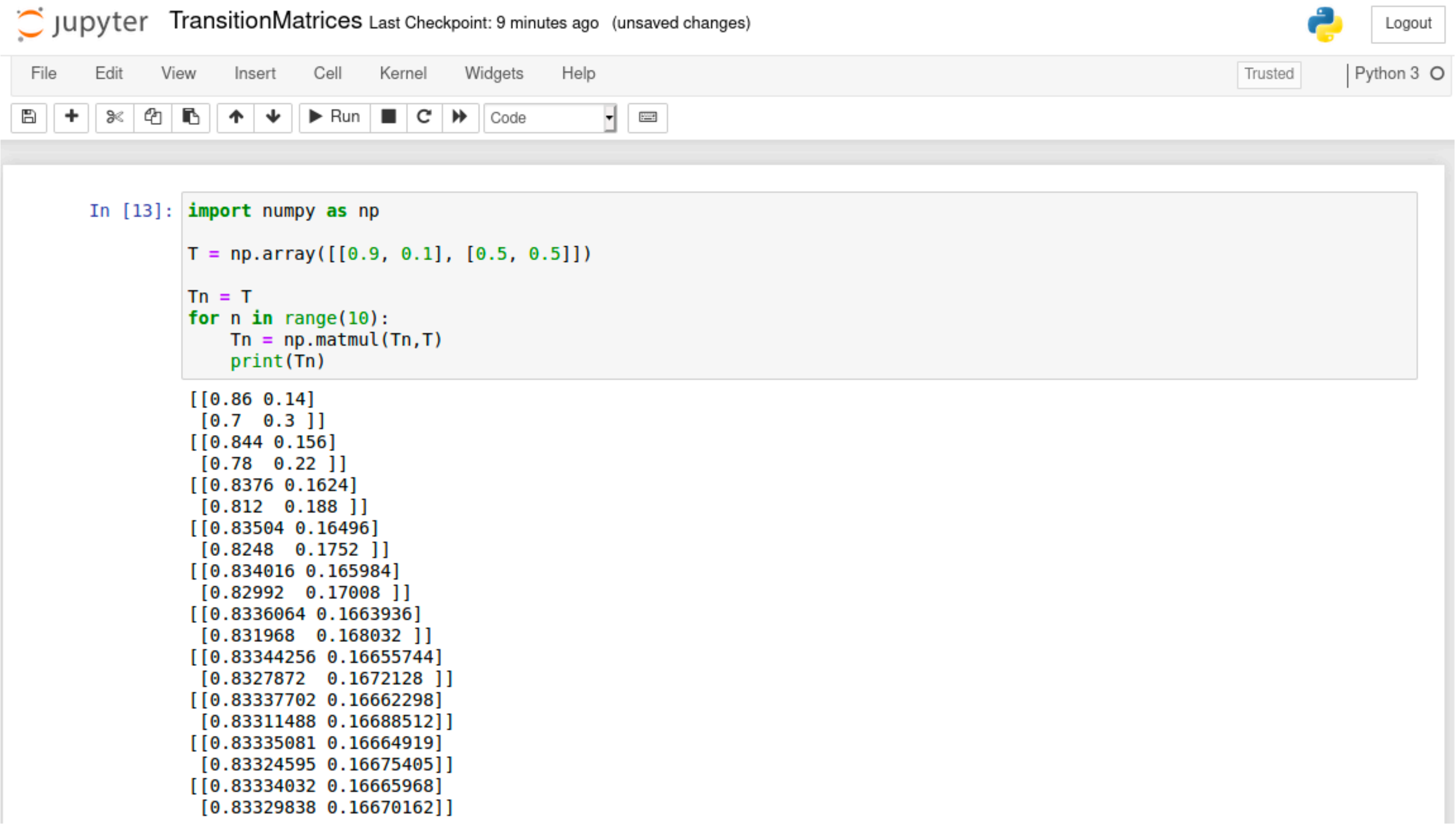
- Given this transition matrix,

$$\begin{bmatrix} 0.9 & 0.1 \\ 0.5 & 0.5 \end{bmatrix},$$

use a Jupyter Notebook to compute the probability after 2, …, 10 steps.

- Hints:
  - It is helpful to define the matrix as a numpy array
    - `import numpy as np`
    - `T = np.array([[0.9, 0.1], [0.5, 0.5]])`
  - use np.matmul instead of the * operator.

Solution: Transition Matrix Powers



In [13]:

```python
import numpy as np

T = np.array([[0.9, 0.1], [0.5, 0.5]])

Tn = T
for n in range(10):
    Tn = np.matmul(Tn,T)
    print(Tn)
```

```
[[0.86 0.14]
 [0.7  0.3 ]]
[[0.844 0.156]
 [0.78  0.22 ]]
[[0.8376 0.1624]
 [0.812  0.188 ]]
[[0.83504 0.16496]
 [0.8248  0.1752 ]]
[[0.834016 0.165984]
 [0.82992  0.17008 ]]
[[0.8336064 0.1663936]
 [0.831968  0.168032 ]]
[[0.83344256 0.16655744]
 [0.8327872  0.1672128 ]]
[[0.83337702 0.16662298]
 [0.83311488 0.16688512]]
[[0.83335081 0.16664919]
 [0.83324595 0.16675405]]
[[0.83334032 0.16665968]
 [0.83329838 0.16670162]]
```

What do you notice about how the transition matrix changes as the number of steps increases?

Uses of Transition Matrices

- the rates of transitions between any pair of states
- the most probable pathways between any pair of states
- the probability of a transition after n steps is P^n.
- the stationary probability of any state

Markov State Models

Markov State Models

- MSMs
  - Markov states = conformational clusters known as *micro states*
  - stationary probability = Boltzmann distribution
  - are similar to chemical kinetics models, but more states and based on molecular simulation opposed to curve fitting
- MSMs are useful because they
  - can combine information from short MD trajectories
  - piece together local equilibria into a global picture

- Introduction to Markov state models by Frank Noe: https://youtu.be/YXppP_QTut8?list=PLych0HcnzSQLi1CQmxiZig9frLGidF70K

pyemma installation and tutorials

- To install pyemma
  - conda env create --pyemma
  - conda activate pyemma
  - conda config --add channels conda-forge
  - conda install pyemma
- To download the tutorials
  - `cd ~/Documents/`
  - `git clone https://github.com/markovmodel/PyEMMA_tutorials`
- http://emma-project.org/latest/tutorial.html#jupyter-notebook-tutorials

References

- [1] Pande, V. S.; Beauchamp, K. A.; Bowman, G. R. Everything You Wanted to Know about Markov State Models but Were Afraid to Ask. Methods (San Diego, Calif.) 2010, 52 (1), 99–105. https://doi.org/10.1016/j.ymeth.2010.06.002.
- [2] Chodera, J. D.; Noé, F. Markov State Models of Biomolecular Conformational Dynamics. Current Opinion in Structural Biology 2014, 25, 135–144. https://doi.org/10.1016/j.sbi.2014.04.002.

Some software

- For MD analysis
  - MDTraj: http://mdtraj.org/1.9.3/index.html
  - ProDy: http://prody.csb.pitt.edu/tutorials/trajectory_analysis/trajectory.html

- For Markov State Models
  - MSMBuilder: http://msmbuilder.org/3.8.0/
  - enspara: https://github.com/bowman-lab/enspara