

## Transcription factor binding

- a single TF binds to a binding site according to simple mass-action kinetic:

$$P(\text{TF bound}) = \frac{[X]}{K + [X]}$$

where  $[X]$  is the concentration and  $K$  the affinity.

- binding is mediated by non-covalent interactions, so  $K$  will depend on salt concentrations
- non-cooperative binding:  $P(\text{TF bound})$  increases linearly with  $[X]$  and saturates at 1 for  $[X] \gg K$

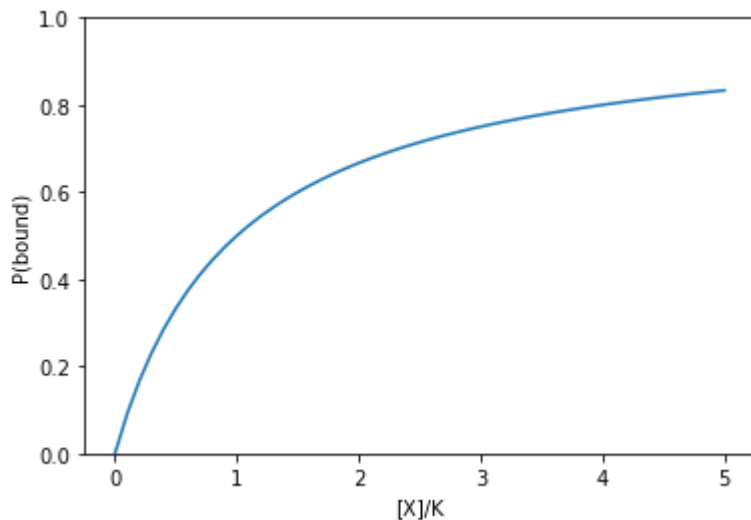
In [1]:

```
import numpy as np
import matplotlib.pyplot as plt

x = np.linspace(0,5,51)
plt.plot(x, x/(1+x))
plt.ylabel('P(bound)')
plt.xlabel('[X]/K')
plt.ylim([0,1])
```

Out[1]:

(0, 1)



## Cooperative binding

- precise regulation requires sharper threshold than the simple first order binding above
- often binding is cooperative and involves multiple TFs (e.g. homo- or hetero-dimers)
- similar to co-operative binding to of oxygen to hemoglobin

Consider transcription factors A and B

- TF-DNA interaction A:  $\epsilon_A$
- TF-DNA interaction B:  $\epsilon_B$
- TF-TF interaction:  $J_{AB}$

The grand partition function is then (comp. Hiller's script)

$$\mathcal{Z} = 1 + ([A]/k_A)e^{-\epsilon_A/kT} + ([B]/k_B)e^{-\epsilon_B/kT} + ([A][B]/k_A k_B)e^{-(\epsilon_A+\epsilon_B+J_{AB})/kT}$$

Multiplying by  $k_A k_B$ , we find for the probability that both A and B are bound:

$$P_{AB} = \frac{[A][B]e^{-(\epsilon_A+\epsilon_B+J_{AB})}}{k_A k_B + \dots + [A][B]e^{-(\epsilon_A+\epsilon_B+J_{AB})}}$$

If cooperation is strong, this simplifies to:

$$P_{AB} \approx \frac{[A][B]e^{-(\epsilon_A+\epsilon_B+J_{AB})}}{k_A k_B + [A][B]e^{-(\epsilon_A+\epsilon_B+J_{AB})}} = \frac{[A][B]}{K + [A][B]}$$

This form of cooperative binding generalizes to  $m$  copies of A and  $n$  copies of B as follows.

$$P_{AB} \approx \frac{[A]^m [B]^n}{K + [A]^m [B]^n}$$

## Hill-functions and cooperativity

Cooperative binding by a single species is often parameterized by so the so called Hill coefficient  $n$ . The probability of activation if the activator is at concentration  $x$  is then

$$h(x) = \frac{x^n}{K + x^n}$$

The higher the Hill-coefficient  $n$ , the more step-like the function is.  $K^{1/n}$  marks the value at which  $h(x) = 0.5$

In [2]:

```
import numpy as np
import matplotlib.pyplot as plt

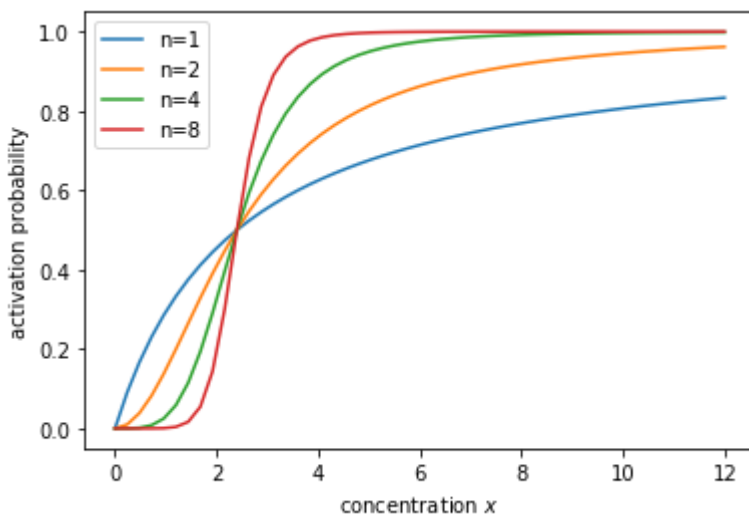
k = 2.4
x = np.linspace(0,5*k,51)

for n in [1,2,4,8]:
    K = k**n
    plt.plot(x, x**n/(K+x**n), label=f"n={n}")

plt.legend()
plt.ylabel("activation probability")
plt.xlabel("concentration $x$")
```

Out[2]:

Text(0.5, 0, 'concentration \$x\$')



## Repression

The above discussion considered binding of activators. If instead the role of the transcription factor is repression, the expression of the gene is given by 1 minus the binding probability.

$$g(x) = 1 - \frac{x^n}{K + x^n} = \frac{K}{K + x^n}$$

## Dig deeper

- We motivated the Hill-coefficients via cooperative binding, where it is naturally an integer. How do these curves behave for fractional  $n$ ?
- For which  $n$  has  $g(t)$  and inflection point?
- How wide is the range of  $x$  values over which  $g(x)$  changes from 0.25 to 0.75 for different  $n$ ? How about 0.05 to 0.95?