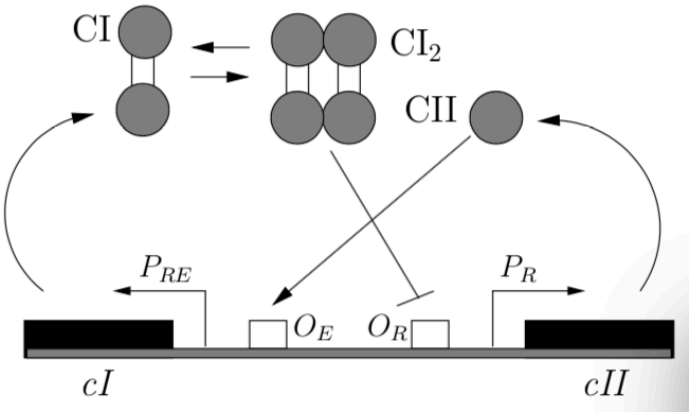
Practical #4: Genetic Circuit Models

The aim of this practical session is to write and execute a (stochastic) biochemical reaction network model for a portion of the **phage λ decision circuit** which is involved in the production of the CI and CII proteins from promoters P_{RE}, respectively P_R .

This portion of the **phage λ decision circuit** is shown in the figure below.



Assuming that there are no CI or CII molecules present initially, CII production is initiated from the P_R promoter, while CI production from P_{RE} only happens at a low basal rate . As CII builds up, it binds to the O_E operator site and activates production of CI molecules from P_{RE}. These CI molecules dimerise and bind to the O_R operator sites, repressing further production of CII. Over time CII degrades, reducing the production rate of CI.

The production of a protein Y from a promoter P can be modelled using 2 reactions :

1. the first reaction denotes *open complex formation,* in which an RNAP molecule reversibly binds to the promoter, to form a complex with default equilibrium constant $K = \frac{k_f}{k_b}$:

$$\mathrm{RNAP} + \mathrm{P} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathrm{S}$$

2. this complex then acts as a modifier in a reaction that models transcription and translation of the protein Y:

$$\mathrm{S} \xrightarrow{k} S + P$$

Question 1: Propose a biochemical reaction network model for the mechanism of CI and CII production described above, knowing that both CI and CII are produced by batches of 10 molecules at a time, and that:

- CI and CII degrade at the same rate, k_d
- the equilibrium constants used for the binding of RNAP to the promoters P_R and P_{RE}, are denoted as K_R, and K_{RE} respectively
- CI is produced at a low basal rate k_b from P_{RE}, when its production is not activated by CII
- CII is produced at its full rate k_o from P_R
- the equilibrium constant for the CI dimerisation reaction is denoted by K_d
- the equilibrium constant of the CII repression reaction whereby one molecule of CI dimer binds to P_R, preventing it from binding to RNAP, is denoted by K_r
- the equilibrium constant of the reaction chain whereby CII activates production of CI from P_{RE} by recruiting RNAP, is given by K_a
- the activated rate of production of CI is given by k_a

Question 2: Translate the network model from Question 1 into a GillesPy2 model, using the parameter values below, and under the assumption that the initial number of RNAP molecules is 30, the initial number of promoters P_R and P_{RE} is 1, and the initial number of molecules for the proteins, CI and CII, is 0.

Simulate the model for different initial copy numbers of CI and CII, and for different values of the (k_f, k_b) pairs that make up the equilibrium constants present in the model (*i.e.*, K_R, K_{RE}, K_d, K_r, K_a). Plot the trajectory of CI and CII in each case, and interpret the results obtained for different parameter values.

$k_d = 0.0075$
$K_R = 0.69422$
$K_{RE} = 0.01$
$k_b = 0.00004$
$k_o = 0.014$
$K_d = 0.1$
$K_r = 0.2165$
$K_a = 0.00161$
$k_a = 0.015$