The Monod-Wyman-Changeux Model

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Contents

Note: this is the MWC.ipynb notebook. The PDF version "The Monod-Wyman-Changeux model" is available here.***

*** Note: incomplete ***

1 Introduction

"For many enzymes, the reaction velocity is not a simple hyperbolic curve, as predicted by the Michaelis–Menten model, but often has a sigmoidal character. This can result from cooperative effects, in which the enzyme can bind more than one substrate molecule but the binding of one substrate molecule affects the binding of subsequent ones" (Keener and Sneyd, 2009), Section 1.4.4.

This note gives a bond graph (Gawthrop and Crampin, 2014) interpretation of such cooperativity and uses the iterative properties of BondGraphTools (Cudmore et al., 2019) to build high-order cooperative systems. These systems are simulated to give steady-state behavior as the order of cooperativity increases.

1.1 Import some python code

The bond graph analysis uses a number of Python modules:

```
In [1]: ## Some useful imports

        import BondGraphTools as bgt
        import numpy as np
        import sympy as sp
        import matplotlib.pyplot as plt
        import IPython.display as disp

        ## Stoichiometric analysis
        import stoich as st

        ## SVG bg representation conversion
        import svgBondGraph as sbg

        ## Modular bond graphs
        import modularBondGraph as mbg

        ## Stoichiometry to BG
        import stoichBondGraph as stbg

        ## Data structure copy
        import copy

        ## Set quiet=False for verbose output
        quiet = True
```

2 Enzyme-catalysed reaction

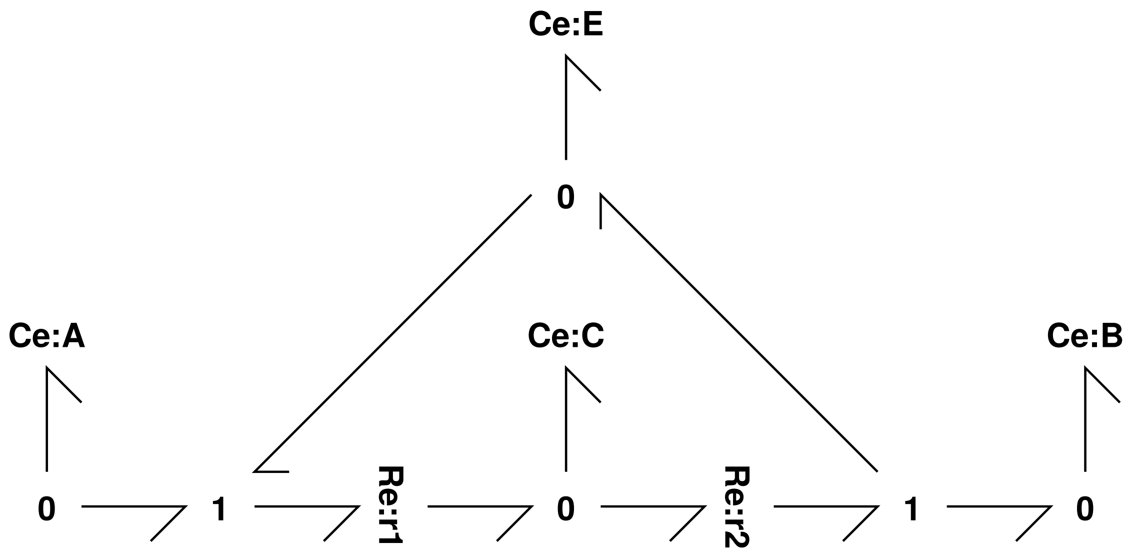
The basic enzyme-catalysed reaction is given in this section. It is the basic building block of cooperative enzyme-catalysed reactions More details are given by (Gawthrop and Crampin, 2014).

```
In [2]: bgt.version
```

```
Out[2]: '0.3.7'
```

```
In [3]: ## Enzyme-catalysed reaction
        sbg.model('RE_abg.svg')
        import RE_abg
        disp.SVG('RE_abg.svg')
```

```
Out[3]:
```



```
In [4]: s = st.stoich(RE_abg.model(),quiet=quiet)
        disp.Latex(st.sprintrl(s,chemformula=True))
```

```
Out[4]:
```

$$A + E \xrightleftharpoons{r_1} C \tag{1}$$

$$C \xrightleftharpoons{r_2} B + E \tag{2}$$

3 Cooperative enzyme-catalysed reaction

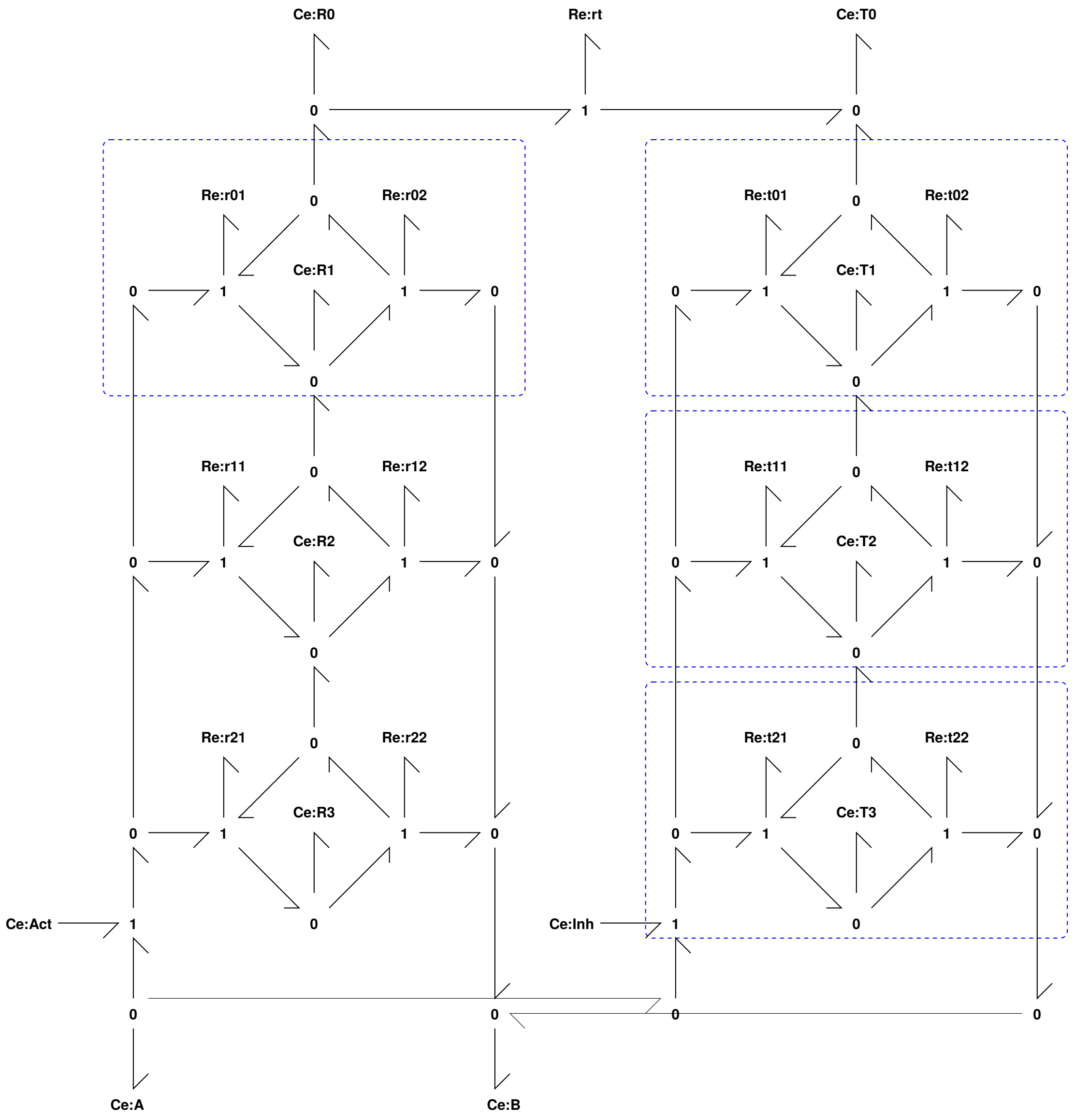
(Keener and Sneyd, 2009), Section 1.4.4, discusses cooperativity. This section gives a bond graph interpretation. This is done in two ways:

1. As a graphical representation of a two-stage cooperative enzyme-catalysed reaction.
2. As a generic representation of an N-stage cooperative enzyme-catalysed reaction using bond-graph tools

3.1 Two-stage cooperative enzyme-catalysed reaction (N=2)

```
In [5]: ## MWC model
        sbg.model('MWC_abg.svg',quiet=quiet)
        import MWC_abg
        disp.SVG('MWC_abg.svg')
```

```
Out[5]:
```



```
In [6]: ss = st.stoich(MWC_abg.model(),quiet=quiet)
        ssc = st.statify(ss,chemostats=['A','Br','Bt','Act','Inh'])
        disp.Latex(st.sprintrl(ss,chemformula=True))
```

```
Chemostat Br is not a model species
Chemostat Bt is not a model species
```

Out[6]:

$$A + Act + R_0 \xrightleftharpoons{r_{01}} R_1 \tag{3}$$
$$R_1 \xrightleftharpoons{r_{02}} B + R_0 \tag{4}$$
$$A + Act + R_1 \xrightleftharpoons{r_{11}} R_2 \tag{5}$$
$$R_2 \xrightleftharpoons{r_{12}} B + R_1 \tag{6}$$
$$A + Act + R_2 \xrightleftharpoons{r_{21}} R_3 \tag{7}$$
$$R_3 \xrightleftharpoons{r_{22}} B + R_2 \tag{8}$$
$$R_0 \xrightleftharpoons{rt} T_0 \tag{9}$$
$$A + Inh + T_0 \xrightleftharpoons{t_{01}} T_1 \tag{10}$$
$$T_1 \xrightleftharpoons{t_{02}} B + T_0 \tag{11}$$
$$A + Inh + T_1 \xrightleftharpoons{t_{11}} T_2 \tag{12}$$
$$T_2 \xrightleftharpoons{t_{12}} B + T_1 \tag{13}$$
$$A + Inh + T_2 \xrightleftharpoons{t_{21}} T_3 \tag{14}$$
$$T_3 \xrightleftharpoons{t_{22}} B + T_2 \tag{15}$$

3.2 Create cooperative enzyme-catalysed reaction of any degree N

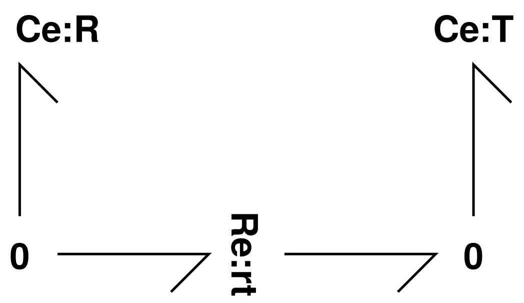
The following code builds an N-stage cooperative enzyme-catalysed reaction using bond-graph tools.

1. N+1 instances of the basic enzyme-catalysed reaction are created and the enzyme and complex renamed.
2. The substrate A, product B and enzymes E1-EN are unified.

```
In [7]: ## Create cooperative enzyme-catalysed reaction of any degree N
        def makeCoop(N=3,R='R',quiet=True):
            r = R.lower()
            Coop = bgt.new(name='Coop')
            for i in range(N+1):
                RE = RE_abg.model()
            RE.name = 'RE'+str(i)
            mbg.rename(RE,{
                          'E':R+str(i),
                          'C':R+str(i+1),
                          'r1':r+str(i)+'1',
                          'r2':r+str(i)+'2'
                          },
                         quiet=quiet)
            Coop.add(RE)

        ## Unify common components
        unified = ['A','B']
        for i in range(N):
            Ri = R+str(i+1)
            unified.append(Ri)
        print('unified =',unified)
        mbg.unify(Coop,unified,quiet=quiet)


        ## Stoichiometry
        chemostats = ['A','B']
        s = st.stoich(Coop,quiet=quiet)
        sc = st.statify(s,chemostats=chemostats)
        if not quiet:
            print(st.sprint(sc,'species'))
            print(st.sprint(sc,'reaction'))

        ## Regenerate flat Coop BG from stoichiometry
        s['name'] = R+'_abg'
        stbg.model(s)

        return s,sc
```

```
In [8]: ## Connecting system
        sbg.model('RT_abg.svg',quiet=quiet)
        import RT_abg
        disp.SVG('RT_abg.svg')
```

```
Out[8]:
```



```
In [9]: srt = st.stoich(RT_abg.model(),quiet=quiet)
        srtc = st.statify(srt,chemostats=['R0','T0'])
        disp.Latex(st.sprintrl(srt,chemformula=True))
```

```
Chemostat R0 is not a model species
Chemostat T0 is not a model species
```

```
Out[9]:
```

$$\mathrm{R} \xrightleftharpoons{rt} \mathrm{T} \tag{16}$$

```
In [10]: ## Create Monod-Wyman-Changeux model
         def makeMWC(N=3,quiet=False):
             MWC = bgt.new(name='MWC')
             sR,sRc = makeCoop(N=N,R='R',quiet=quiet)
             sT,sRT = makeCoop(N=N,R='T',quiet=quiet)
             import R_abg
             import T_abg
             import RT_abg

             MWC.add(R_abg.model(),T_abg.model(),RT_abg.model())

         #      ## Unify common components
         #      unified = ['A','B','R0','T0']

         #     MWC.add(R_abg.model(),T_abg.model())

             ## Unify common components
             unified = ['A','B','R','T']

             mbg.unify(MWC,unified,quiet=False)

             ## Stoichiometry
             chemostats = ['A','B']
             s = st.stoich(MWC,quiet=quiet)
             sc = st.statify(s,chemostats=chemostats)
             if not quiet:
                 print(st.sprint(sc,'species'))
                 print(st.sprint(sc,'reaction'))

             return s,sc,MWC
```

3.2.1 Generate equations for $N = 2$

Note that these equations are identical to those of the explicit bondgraph.

```
In [11]: ### Generate equations for N=2
         s,sc,MWC = makeMWC(N=2,quiet=quiet)
         disp.Latex(st.sprintrl(s,chemformula=True))
```

```
unified = ['A', 'B', 'R1', 'R2']
unified = ['A', 'B', 'T1', 'T2']
Unifying components in: MWC
Creating: Ce:A and 0:A_jun in MWC
Creating: Ce:B and 0:B_jun in MWC
Creating: Ce:R and 0:R_jun in MWC
Creating: Ce:T and 0:T_jun in MWC
Exposing: Ce:A in R_abg and connecting to 0:A_jun
Exposing: Ce:B in R_abg and connecting to 0:B_jun
Exposing: Ce:A in T_abg and connecting to 0:A_jun
Exposing: Ce:B in T_abg and connecting to 0:B_jun
Exposing: Ce:R in RT and connecting to 0:R_jun
Exposing: Ce:T in RT and connecting to 0:T_jun
```

```
Out[11]:
```

$$R_0 + A \xrightleftharpoons{r_{01}} R_1 \tag{17}$$

$$R_1 \xrightleftharpoons{r_{02}} R_0 + B \tag{18}$$

$$R_1 + A \xrightleftharpoons{r_{11}} R_2 \tag{19}$$

$$R_2 \xrightleftharpoons{r_{12}} R_1 + B \tag{20}$$

$$R_2 + A \xrightleftharpoons{r_{21}} R_3 \tag{21}$$

$$R_3 \xrightleftharpoons{r_{22}} R_2 + B \tag{22}$$

$$T_0 + A \xrightleftharpoons{t_{01}} T_1 \tag{23}$$

$$T_1 \xrightleftharpoons{t_{02}} T_0 + B \tag{24}$$

$$T_1 + A \xrightleftharpoons{t_{11}} T_2 \tag{25}$$

$$T_2 \xrightleftharpoons{t_{12}} T_1 + B \tag{26}$$

$$T_2 + A \xrightleftharpoons{t_{21}} T_3 \tag{27}$$

$$T_3 \xrightleftharpoons{t_{22}} T_2 + B \tag{28}$$

$$R \xrightleftharpoons{rt} T \tag{29}$$

3.2.2 Generate pathway equations for $N = 2$

Pathways are generated using the approach of (Gawthrop and Crampin, 2017).

```
In [12]: sp = st.path(s,sc)
         print(st.sprintp(sc))
         disp.Latex(st.sprintrl(sp))
```

```
6 pathways
0:  + r01 + r02
1:  + r11 + r12
2:  + r21 + r22
3:  + t01 + t02
4:  + t11 + t12
5:  + t21 + t22
```

Out[12]:

$$A \Leftrightarrow B \tag{30}$$
$$A \Leftrightarrow B \tag{31}$$
$$A \Leftrightarrow B \tag{32}$$
$$A \Leftrightarrow B \tag{33}$$
$$A \Leftrightarrow B \tag{34}$$
$$A \Leftrightarrow B \tag{35}$$

3.3 Steady-state properties

The steady state properties are investigated using dynamic simulation where slowly varing exogenous quantities are used to induce quasi-steady-state behaviour. In each case, the variable is at a constant value to start with followed by a slowly increasing ramp. The response after the initial reponse is plotted to remove artefacts due to the initial transient.

All parameters are unity except for $K_B = 0.01$ (to approximate an irreversible reaction) and initial states are chosen so that the total enzyme is $e_0 = 1$.

3.3.1 Set up some parameters for simulation

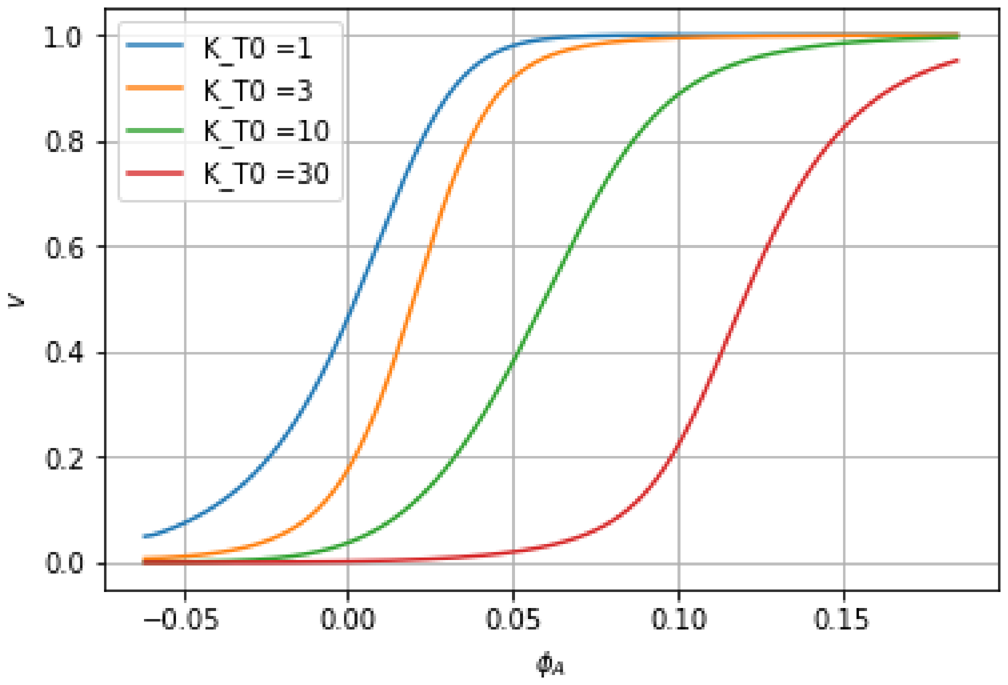
```
In [13]: ## Set up some parameters for simulation
         def setParameter(ss,N,K_R0,K_T0,X_Act,X_Inh):

             e0 = 1/2

             ## Set up the non-unit parameters and states
             parameter = {}


             K_i = 1/(K_R0**(N+1))
             for i in range(N+2):
                 Ki = 'K_R'+str(i)
                 #print('Setting:', Ki)
```

```
            parameter[Ki] = K_i
            K_i *= K_R0

        K_i = 1/(K_T0**(N+1))
        if 'T0' in s['species']:
            for i in range(N+2):
                Ki = 'K_T'+str(i)
                #print('Setting:', Ki)
                parameter[Ki] = K_i
                K_i *= K_T0

        ## Set product constant to a small value
        ## to make the RCR approximately irreversible
        K_B = 1e-10
        parameter['K_B'] = K_B
#       parameter['K_Br'] = K_B
#       parameter['K_Bt'] = K_B

#       parameter['K_R00'] = parameter['K_R0']
#       parameter['K_T00'] = parameter['K_T0']
#      parameter['K_Inh'] = 100

        ## States
        X0 = np.ones(ss['n_X'])
        X0[ss['spec_index']['Act']] = X_Act
        X0[ss['spec_index']['Inh']] = X_Inh

        ## Set total enzyme to e0
        for i in range(N+2):
            Ri = 'R'+str(i)
            X0[ss['spec_index'][Ri]] = (e0/(N+2))

        if 'T0' in s['species']:
            for i in range(N+2):
                Ti = 'T'+str(i)
                X0[ss['spec_index'][Ti]] = (e0/(N+2))

        return parameter,X0
```

3.3.2 Vary substrate concentration x_A for various K_{T0}

In [14]:
```
## Simulation
## Vary x_A

##Time
quiet = True
t_max = int(1e5)
t = np.linspace(0,t_max,100000)
```

```
t_0 = 100
t_1 = t_max-t_0
i_max = len(t)
i_0 = int(i_max*t_0/t_max)
i_1 = i_max-i_0

## Chemostats: vary x_A
x_max = 1e3
x_min = 1e-1

A_chemo = '{3} + ({0}-{3})*np.heaviside(t-{1},1)*((t-{1})/{2})'.format(x_max,t_0,t_1,x_
X_chemo =  {'A':A_chemo}

K_R0 = 1
K_T0 = 1


for K_T0 in [1,3,10,30]:
    N = 2

    X_Act = K_T0
    X_Inh = 1

    parameter,X0 = setParameter(ss,N,K_R0,K_T0,X_Act,X_Inh)

    dat = st.sim(ss,sc=ssc,t=t,parameter=parameter,X0=X0,X_chemo=X_chemo,quiet=quiet)
    phi_A = dat['phi'][:,ss['spec_index']['A']]
    dX = ss['N']@(dat['V'].T)
    dX_B = dX[ss['spec_index']['B'],:]
    V_B = dX_B[-i_1:]

    ## Plot flow v. x_A
    grey = '0.8'
    plt.plot(phi_A[-i_1:],V_B,label = 'K_T0 ='+str(K_T0))
plt.grid()
plt.legend()
#plt.ylim((0,e0))
#plt.xlim((0,x_max))
#plt.legend(['N=0 (theory)']+['N='+str(i) for i in NN]+['MWC'])
plt.xlabel('$\phi_A$')
plt.ylabel('$v$')
plt.show()
```



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Peter J. Gawthrop and Edmund J. Crampin. Energy-based analysis of biomolecular pathways. *Proceedings of the Royal Society of London A: Mathematical, Physical and Engineering Sciences*, 473 (2202), 2017. ISSN 1364-5021. doi:10.1098/rspa.2016.0825. Available at arXiv:1611.02332.

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