Allosteric inhibition as a control actuator: loop-gain analysis

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February 21, 2020

Contents

Note: this is the Allosteric.ipynb notebook. The PDF version "Allosteric inhibition as a control actuator: loop-gain analysis" is available here.

1 Introduction

Using the methods of control theory to examine and reexamine the behaviour of living systems is well-established (Craik, 1947) (Wiener, 1961) (Bayliss, 1966) (Savageau, 2009) (Jagacinski and Flach, 2003) (Iglesias and Ingalls, 2010) (Wellstead et al., 2008) (Drion et al., 2015) (Del Vecchio, 2013). This notebook examines the enzyme-catalysed reaction as a control actuator and its behavior within a feedback loop controlling product concentration. The feedback mechanism used is *Allosteric inhibition* - see section 1.4.3 (Keener and Sneyd, 2009).

- The notebook fECR looks at an alternative feedback mechanism : feedback inhibition.
- As discussed in the sequel, feedback inhibition is a special case of allosteric inhibition.
- As discussed in the notebook fECR, the control methodology is based on Linearisation.
- This notebook introduces a novel method for deducing the *feedback loop-gain* $L(s)$ from the bond graph describing the biomolecular system. $L(s)$ is a crucial component of feedback control analysis.

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 sym
        import matplotlib.pyplot as plt
        import IPython.display as disp

        ## Stoichiometric analysis
        import stoich as st

        ## SVG bg representation conversion
        import svgBondGraph as sbg

        ## Control systems package
        import control as con

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

        ## Set slycot=True if slycot is installed (see control module)
        slycot=True

        ## For reimporting: use imp.reload(module)
        import importlib as imp
```

```
## Printing options
np.set_printoptions(precision=3)
fmt = '{:5.3f}'

## Allow output from within functions
from IPython.core.interactiveshell import InteractiveShell
InteractiveShell.ast_node_interactivity = "all"

## Minreal (minimum realisation algorithm) tolerance
tol = 1e-2

## Chemostat EM and CM
chemostatEMCM = True
```

1.2 Derive stoichiometry from bond graph

```
In [2]: def stoichiometry(abg,chemostats=[]):
            s = st.stoich(abg.model(),quiet=quiet)
            sc = st.statify(s,chemostats=chemostats)
            return s,sc
```

2 Enzme catalysed reaction with allosteric inhibition

2.1 Bond graph model

- **Ce:A**: substrate
- **Ce:B**: product
- **Ce:B0**: product sink
- **Ce:E**: enzyme
- **Ce:C**: enzyme bound to A
- **Ce:F** and **Ce:G**: species pumping the reaction
- **Ce:B**: product
- **Ce:EM**: enzyme bound to M
- **Ce:CM**: complex C bound to M
- Corresponding reactions are:

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

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

$$B \xrightleftharpoons{r_3} B_0 \tag{3}$$

$$CM \xrightleftharpoons{ra} A + EM \tag{4}$$

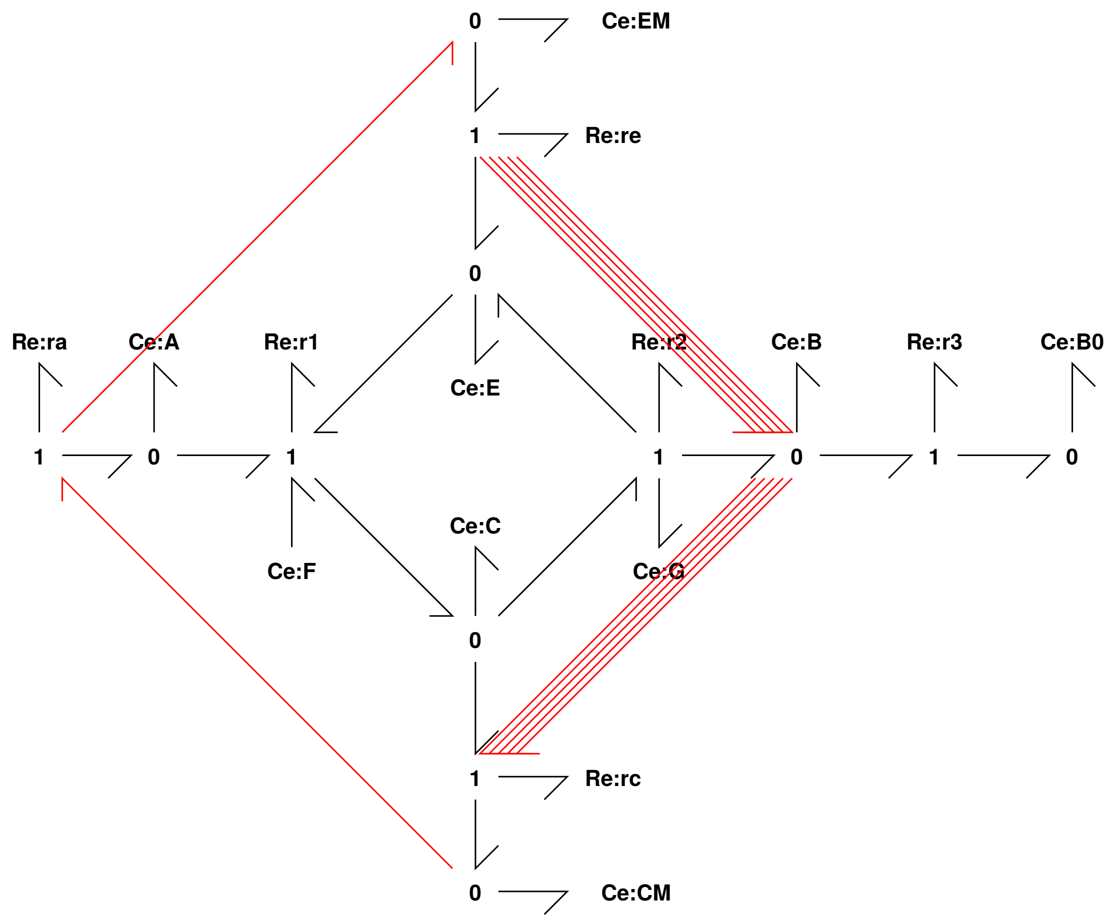
$$5\,B + C \xrightleftharpoons{rc} CM \tag{5}$$

$$EM \xrightleftharpoons{re} 5\,B + E \tag{6}$$

```
In [3]: sbg.model('aiRE_abg.svg',quiet=quiet)
        import aiRE_abg
```

```
abg = aiRE_abg
disp.SVG('aiRE_abg.svg')
```

Out[3]:



```
In [4]: ## Stoichiometry
        #chemostats=['A','B0','F','G','EM','CM']
        chemostats=['A','B0','F','G']
        if chemostatEMCM:
            chemostats += ['EM','CM']

        s,sc = stoichiometry(abg,chemostats=chemostats)

        print('Reactions:')
        disp.Latex(st.sprintrl(s,chemformula=False))
        sp = st.path(s,sc)
```

```
Reactions:
```

Out[4]:

$$A + E + F \Leftrightarrow C \tag{7}$$
$$C \Leftrightarrow B + E + G \tag{8}$$
$$B \Leftrightarrow B0 \tag{9}$$
$$CM \Leftrightarrow A + EM \tag{10}$$
$$5B + C \Leftrightarrow CM \tag{11}$$
$$EM \Leftrightarrow 5B + E \tag{12}$$

2.2 Numerical parameters

In [5]:
```
## Parameters
X0_A = 1
K_A = 1
K_B = 1
K_C = 1
K_E = 1
K_F = 1e2
K_G = 1/K_F

K_EM = 1
K_CM = 1

kappa = 1
kappa_r1 = kappa
kappa_r2 = kappa

## Open-loop
kappa_ra = 0
kappa_rc = 0
kappa_re = 0

K_B0 = 1
X0_B0 = 1e-6
kappa_r3 = 1

pars = ['X0_A','K_A','K_B','K_C','K_E','K_F','K_G',
        'K_EM','K_CM',
        'kappa_r1','kappa_r2','kappa_ra','kappa_rc','kappa_re',
        'K_B0','X0_B0','kappa_r3']
parameter = {}
for par in pars:
    parameter[par] = eval(par)

if not quiet:
    print('Parameters',parameter)
```

2.3 Utility functions

```
In [6]: def plotStep(tf,chemo,spec,T):

            t,y = con.step_response(tf,T=T)
            plt.plot(t,y)
            plt.grid()
            plt.xlabel('t')
            plt.ylabel('x_B')
            plt.title('Step response from '+chemo+' to '+spec)
            plt.show()

        def showTF(tf):
            ## Show info
            print(tf)
            in_gain_X = con.dcgain(tf)
            print('\tgain:',fmt.format(in_gain_X))
            print('\tpoles:', con.pole(tf))
            print('\tzeros:', con.zero(tf))

        def extractTF(TF,chemo,spec):

            ## Index of product
            species = s['species']
            i_prod = species.index(spec)

            ## Index of input
            i = chemostats.index(chemo)

            ## Extract tf
            print('\nTransfer function from','x_'+chemo,'to','x_'+spec)
            tf = con.minreal(TF[i_prod,i])

            showTF(tf)

            return tf

        def extractTFflow(TF,chemo,chemostats,reac):

            ## Index of reaction
            reaction = s['reaction']
            i_v = reaction.index(reac)

            ## Index of input
            i = chemostats.index(chemo)

            ## Extract tf
            print('\nTransfer function from','x_'+chemo,'to','v_'+reac)
```

```
    tf = con.minreal(TF[i_v,i])

    showTF(tf)

    return tf
```

3 Closed-loop analysis

The function **ClosedLoop** derives the closed-loop properteis of the system from the bond graph model in the following steps:

- Extract stoichiometry
- Simulate the system to give a steady state
- linearise the closed-loop system about this steady state to give:
- the multivariable transfer function relating chemostats to species states
- the multivariable transfer function relating chemostats to reaction flows
- extract the scalar transfer functions relating the 'disturbance' x_{B0} to
  - the product state x_B
  - the 'actuator' flow v_{r2}

```
In [7]: def ClosedLoop(abg,chemostats,parameter,t_step,quiet=False):
            ## Analyse the system

            ## Stoichiometry
            s,sc = stoichiometry(abg,chemostats=chemostats)

            ## Steady-state simulation
            t = np.linspace(0,1000,1000)
            ssdat = st.sim(s,sc=sc,t=t,parameter=parameter,quiet=quiet)

            ## Use the final value as the steady-state
            x_ss = ssdat['X'][-1,:]

            if not quiet:
                print(s['species'])
                print('x_ss =', x_ss)

            ##Linearise
            SysX = st.lin(s,sc,x_ss=x_ss,parameter=parameter,outvar='X',quiet=quiet)
            SysV = st.lin(s,sc,x_ss=x_ss,parameter=parameter,outvar='V',quiet=quiet)

            ## Multivariable transfer functions
            TF = con.ss2tf(SysX)
            TFV = con.ss2tf(SysV)

            ## Scalar transfer function to x_B
            tf_B0 = extractTF(TF,'B0','B')
            t,x_B = con.step_response(tf_B0,T=t_step)

            ## Scalar transfer function to v_r2
            tf_v2 = extractTFflow(TFV,'B0',chemostats,'r2')
            t,v_r2 = con.step_response(tf_v2,T=t_step)

            return x_B,v_r2,x_ss
```

3.1 Open-loop system

Setting $\kappa_{re} = \kappa_{rc} = \kappa_{ra} = 0$ prevents flow through the inhibition system and thus feedback is prevented. The system is open-loop.

- the closed-loop transfer function relating x_{B0} to x_B is $\frac{1}{s+1}$. This has a steady-state gain of unity: the disturbance is not reduced.
- the closed-loop transfer function relating x_{B0} to x_{r2} is ≈ 0. It becomes zero as $K_F \to \infty$. There is no feednack.

```
In [8]: ## Open loop
        t_step = np.linspace(0,20,100)
        print("Open loop")

        parameter['kappa_re'] = 0
        parameter['kappa_rc'] = 0
        parameter['kappa_ra'] = 0

        x_ol,v_ol,x_ss_ol = ClosedLoop(abg,chemostats,parameter,t_step,quiet=quiet)
```

```
Open loop

Transfer function from x_B0 to x_B
1 states have been removed from the model

  1
-----
s + 1

        gain: 1.000
        poles: [-1.]
        zeros: []

Transfer function from x_B0 to v_r2
0 states have been removed from the model

-0.0003921 s - 0.0396
---------------------
 s^2 + 103 s + 102.1
```

```
        gain: -0.000
        poles: [-102.02   -1.  ]
        zeros: [-101.]
```

3.2 Feedback inhibition

Setting $\kappa_{rc} = \kappa_{ra} = 0$ and $\kappa_{re} = 1$ restricts feedback to the path through re and is thus equivalent to feedback inhibition.

- the closed-loop transfer function relating x_{B0} to x_B has a steady-state gain of 0.167; the effect of the disturbance is reduced by feedback.
- the closed-loop transfer function relating x_{B0} to x_{r2} has a steady-state gain of -0.833; this is negative feedback.

```
In [9]: ## Feedback inhibition
        print('Feedback inhibition')

        parameter['kappa_re'] = 1
        parameter['kappa_rc'] = 0
        parameter['kappa_ra'] = 0

        x_fi,v_fi,x_ss_fi = ClosedLoop(abg,chemostats,parameter,t_step,quiet=quiet)
```

```
Feedback inhibition

Transfer function from x_B0 to x_B
0 states have been removed from the model

      s^2 + 128.1 s + 52.09
--------------------------------
s^3 + 142.1 s^2 + 1509 s + 312.6

        gain: 0.167
        poles: [-130.551  -11.329   -0.211]
        zeros: [-127.657   -0.408]

Transfer function from x_B0 to v_r2
0 states have been removed from the model

-0.0003839 s^2 + 0.001222 s - 260.5
-----------------------------------
  s^3 + 142.1 s^2 + 1509 s + 312.6

        gain: -0.833
        poles: [-130.551  -11.329   -0.211]
        zeros: [1.592+823.657j 1.592-823.657j]
```

3.3 Allosteric inhibition

Setting $\kappa_{re} = \kappa_{rc} = \kappa_{ra} = 1$ releases all feedback paths.

- the closed-loop transfer function relating x_{B0} to x_B has a steady-state gain of 0.166; the effect of the disturbance is reduced by feedback.
- the closed-loop transfer function relating x_{B0} to x_{r2} has a steady-state gain of -0.834; this is negative feedback.

```
In [10]: ## Allosteric inhibition
         print('Allosteric inhibition')

         parameter['kappa_re'] = 1
         parameter['kappa_rc'] = 1
         parameter['kappa_ra'] = 1

         x_ai,v_ai,x_ss_ai = ClosedLoop(abg,chemostats,parameter,t_step,quiet=quiet)
```

```
Allosteric inhibition

Transfer function from x_B0 to x_B
1 states have been removed from the model

      s + 1.74
--------------------
s^2 + 47.5 s + 10.51

        gain: 0.166
        poles: [-47.273  -0.222]
        zeros: [-1.74]

Transfer function from x_B0 to v_r2
0 states have been removed from the model

-0.0003179 s^2 - 8.734 s - 910.2
--------------------------------
s^3 + 151.2 s^2 + 4938 s + 1091

        gain: -0.834
        poles: [-103.753  -47.273   -0.222]
        zeros: [-27366.453   -104.613]
```

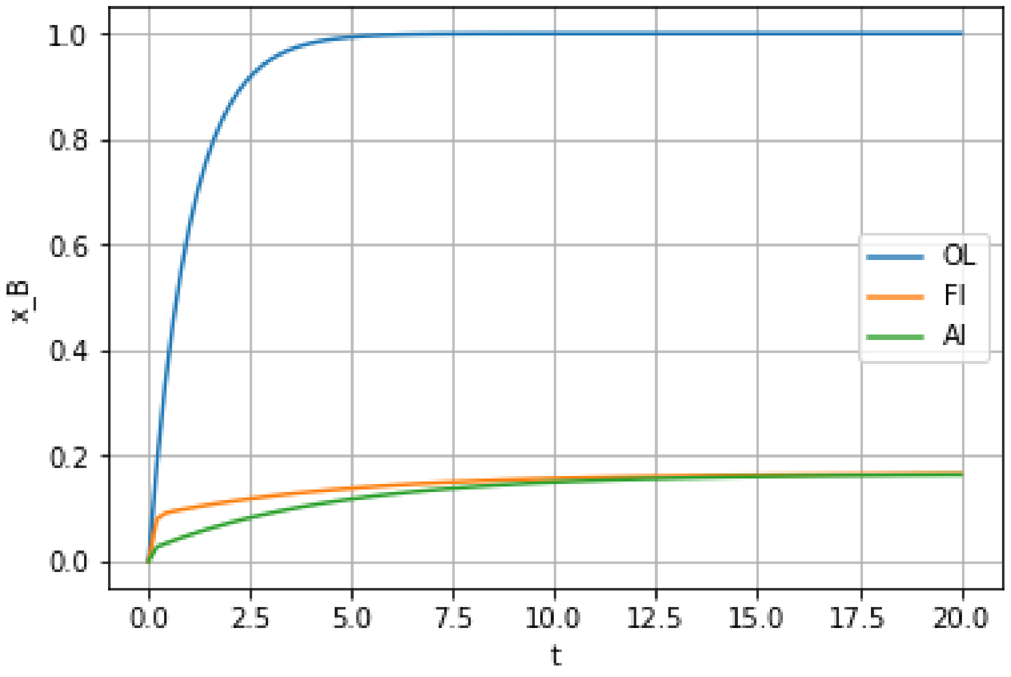
3.4 Comparison of step responses

The product state x_B and feedback flow v_2 are plotted against time for a unit step in the disturbance x_{B0} for each of the three scenarios. In this case, both forms of feedback attenuate the disturbance by about the same amount.

```
In [11]: def Plot(t_step,x_ol,x_fi,x_ai):
             plt.plot(t_step,x_ol,label='OL')
             plt.plot(t_step,x_fi,label='FI')
             plt.plot(t_step,x_ai,label='AI')
             plt.legend()
             plt.grid()
             plt.xlabel('t')
             plt.show()
```

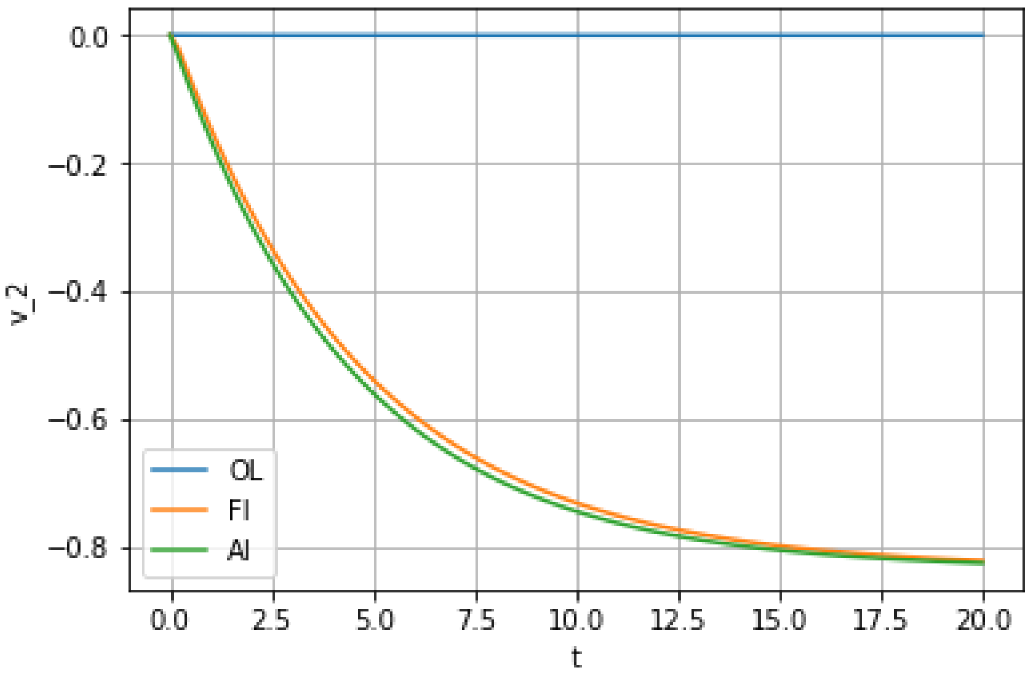
```
In [12]: plt.ylabel('x_B')
         Plot(t_step,x_ol,x_fi,x_ai)
```

```
Out[12]: Text(0,0.5,'x_B')
```



```
In [13]: plt.ylabel('v_2')
         Plot(t_step,v_ol,v_fi,v_ai)
```

```
Out[13]: Text(0,0.5,'v_2')
```



4 Loop-gain analysis

- The product component **Ce:B** is converted into a chemostat. This 'breaks the loop' and enables the open-loop transfer functions relating x_B to the various flows impinging on the corresponding **0** junction to be computed. In this case the relevant flows are:
  - v_{r2} - the main feedback path
  - v_{r3} - the product flow flow absorbed by **Ce:B0**
  - $5v_{re}$ - the flow transiently absorbed by **Ce:EM**
  - $5v_{ce}$ - the flow transiently absorbed by **Ce:CM**
- The function LoopGain

```
In [14]: def LoopGain(abg,chemostats,parameter,x_ss,quiet=False):
             """Compute the loop gain tf"""

             ## Add the chemostat for B and recompute stoichiometry
             chemostatsL = chemostats+['B']
             sL,scL = stoichiometry(abg,chemostats=chemostatsL)

             ## Linearise using the appropriate steady-state x_ss
             SysL = st.lin(sL,scL,x_ss=x_ss,parameter=parameter,outvar='V',quiet=quiet)

             ## The multivariable transfer function
             TFL = con.ss2tf(SysL)
```

```
## Stoichiometry of feedback
N = sL['N'] # Stoichiometric matrix
i_B = sL['species'].index('B')
N_B = N[i_B,:] # Row of N corresponding to B

## Indices of reactions impinging on Ce:
j_FB = np.nonzero(N_B)[0][:]

## Reactions impinging on B and the transfer functions
reaction = sL['reaction']
R = []
FB = {}
fb = 0
for j in j_FB:
    r = reaction[j]
    R.append(r)
    FB[r] = extractTFflow(TFL,'B',chemostatsL,r)
    fb = con.parallel(fb,-N_B[j]*FB[r])
print('\nRelevant reactions:', R)

## Total feedback transfer function
print('Net feedback')
fb = con.minreal(fb,tol=tol)
showTF(fb)

## Transfer function of CE:B
G = con.tf([K_B],[1,0])
print("Forward gain to B")
showTF(G)

print('Loop gain L')
L = con.series(G,fb)
print(L)

print("Closed loop")
LL = con.minreal(con.feedback(G,sys2=fb),tol=tol)
showTF(LL)

## Plot Bode diagram
print('Bode diagram')
w = np.logspace(-1,3)
mag,phase,ww = con.freqresp(L,w)
plt.loglog(w,mag[0,0])
plt.xlabel('$\omega$ (rad/sec)')
plt.ylabel('$|L|$')
plt.grid()
```

```
        plt.show()
        plt.semilogx(w,phase[0,0]*180/np.pi)
        plt.xlabel('$\omega$ (rad/sec)')
        plt.ylabel('arg $L$ (deg)')
        plt.grid()
        plt.show()
```

4.1 Open-loop system

Setting $\kappa_{re} = \kappa_{rc} = \kappa_{ra} = 0$ prevents flow through the inhibition system and thus feedback is prevented. The system is open-loop.

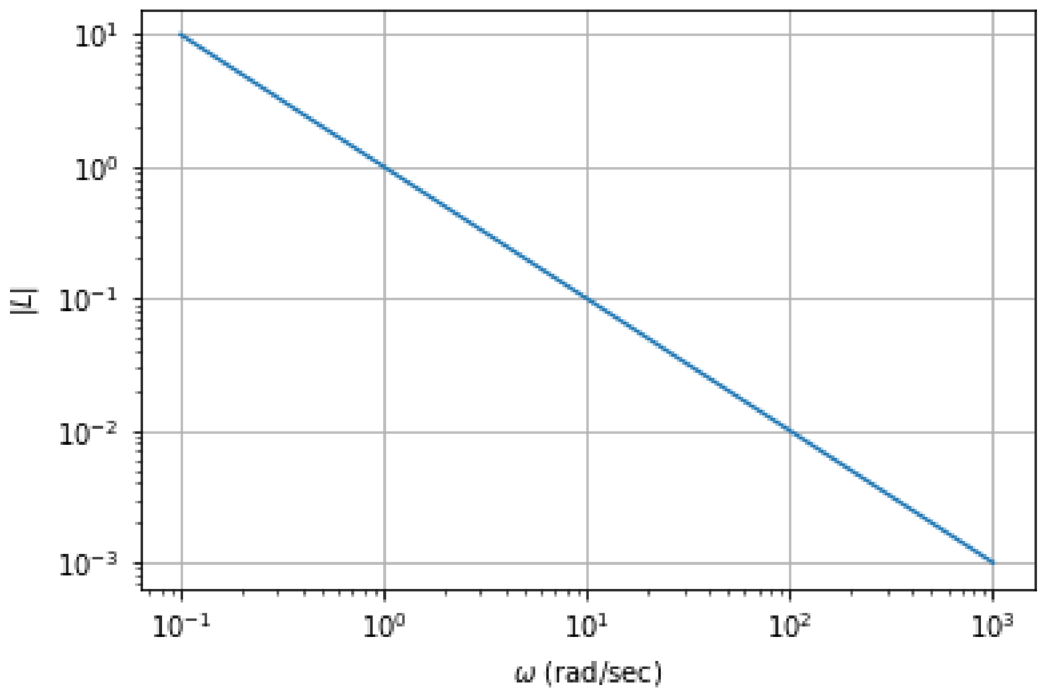
- The only non-zero feedback path is via v_{r3}.
- The closed-loop system derived from L is the same as given above.

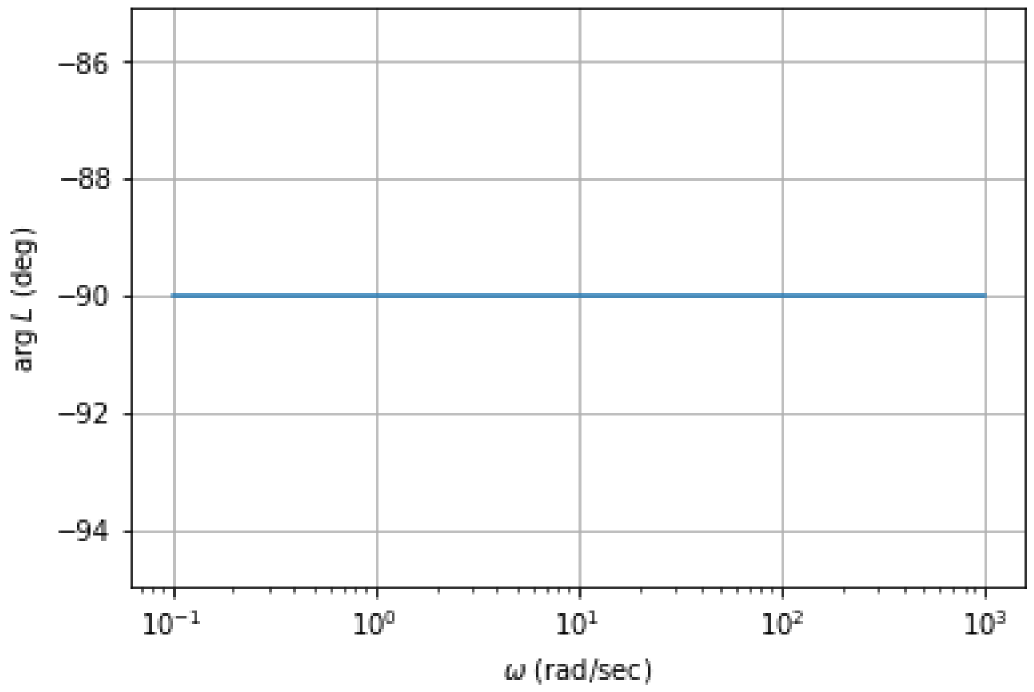
```
In [15]: ## Open loop
         print('Open loop')
         parameter['kappa_re'] = 0
         parameter['kappa_rc'] = 0
         parameter['kappa_ra'] = 0

         LoopGain(abg,chemostats,parameter,x_ss_ol,quiet=quiet)
```

```
Open loop

Transfer function from x_B to v_r2
0 states have been removed from the model

-0.0003921 s - 0.0396
---------------------
       s + 102

        gain: -0.000
        poles: [-102.02]
        zeros: [-101.]

Transfer function from x_B to v_r3
1 states have been removed from the model

1
-
1

        gain: 1.000
        poles: []
        zeros: []

Transfer function from x_B to v_rc
0 states have been removed from the model
```

```
0
-
1

        gain: 0.000
        poles: []
        zeros: []

Transfer function from x_B to v_re
0 states have been removed from the model

0
-
1

        gain: 0.000
        poles: []
        zeros: []

Relevant reactions: ['r2', 'r3', 'rc', 're']
Net feedback
1 states have been removed from the model

1
-
1

        gain: 1.000
        poles: []
        zeros: []
Forward gain to B

1
-
s

        gain:   inf
        poles: [0.]
        zeros: []
Loop gain L

1
-
s

Closed loop
0 states have been removed from the model
```

```
  1
-----
s + 1

        gain: 1.000
        poles: [-1.]
        zeros: []
Bode diagram
```





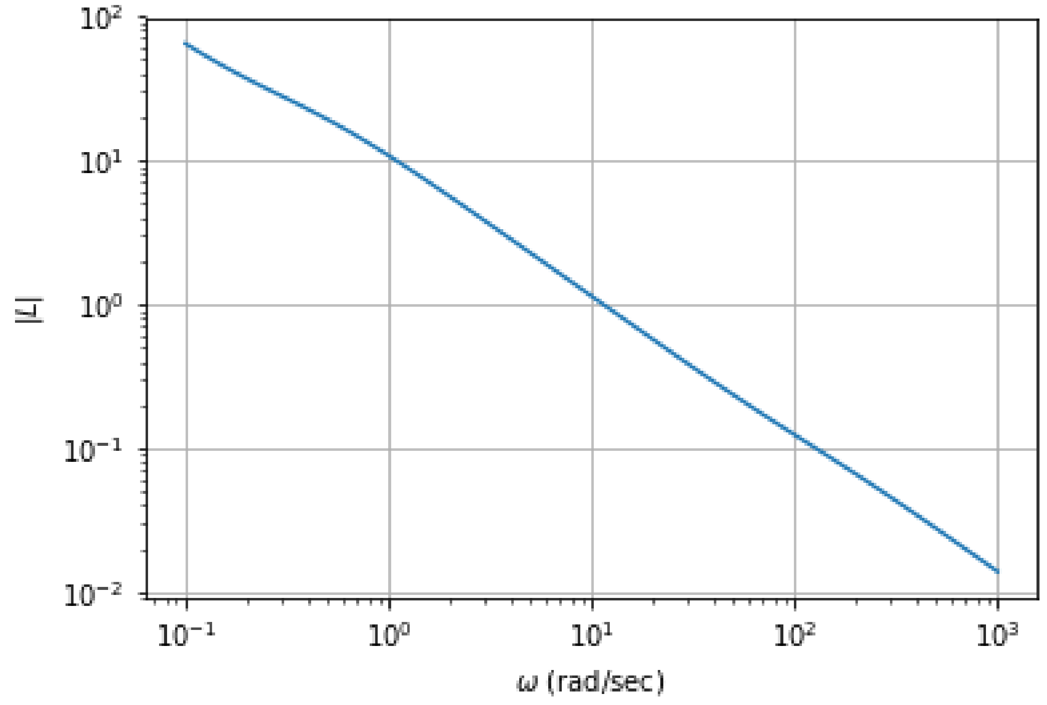
4.2 Feedback inhibition

Setting $\kappa_{rc} = \kappa_{ra} = 0$ and $\kappa_{re} = 1$ restricts feedback to the path through re and is thus equivalent to feedback inhibition. - In addition to the non-zero feedback path is via v_{r3}, the feedback paths through v_{r2} (the main feedback path) and via v_{re} are non-zero. - The main feedback path has a steady-state gain of 5. - The steady-state gain via v_{re} is zero - the effect of this path is transient. - The closed-loop system derived from L is the same as given above.

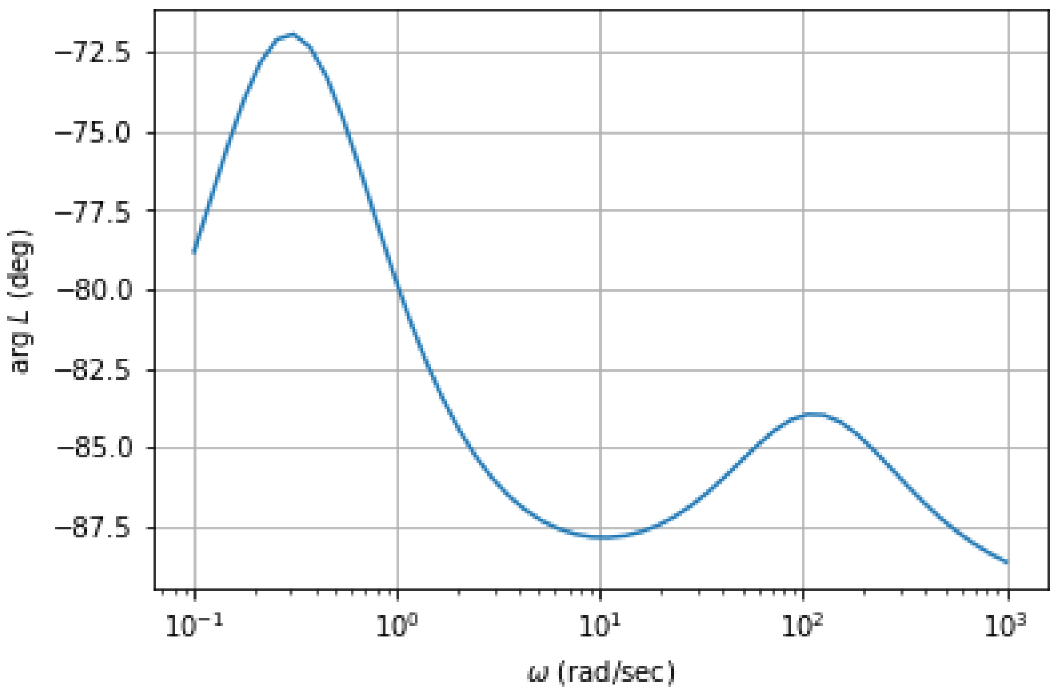
```
In [16]: ## Feedback inhibition
         print('Feedback inhibition')

         parameter['kappa_re'] = 1
         parameter['kappa_rc'] = 0
         parameter['kappa_ra'] = 0

         LoopGain(abg,chemostats,parameter,x_ss_fi,quiet=quiet)
```

```
Feedback inhibition

Transfer function from x_B to v_r2
0 states have been removed from the model

-0.0003839 s^2 + 0.001222 s - 260.5
-----------------------------------
```

```
       s^2 + 128.1 s + 52.09

        gain: -5.000
        poles: [-127.657   -0.408]
        zeros: [1.592+823.657j 1.592-823.657j]

Transfer function from x_B to v_r3
2 states have been removed from the model

1
-
1

        gain: 1.000
        poles: []
        zeros: []

Transfer function from x_B to v_rc
0 states have been removed from the model

0
-
1

        gain: 0.000
        poles: []
        zeros: []

Transfer function from x_B to v_re
0 states have been removed from the model

-2.605 s^2 - 265.8 s - 1.137e-13
--------------------------------
      s^2 + 128.1 s + 52.09

        gain: -0.000
        poles: [-127.657   -0.408]
        zeros: [-1.020e+02 -4.278e-16]

Relevant reactions: ['r2', 'r3', 'rc', 're']
Net feedback
2 states have been removed from the model

14.03 s^2 + 1457 s + 312.6
--------------------------
  s^2 + 128.1 s + 52.09

        gain: 6.000
        poles: [-127.657   -0.408]
        zeros: [-103.655   -0.215]
Forward gain to B

1
-
s

        gain:   inf
        poles: [0.]
        zeros: []
Loop gain L

14.03 s^2 + 1457 s + 312.6
--------------------------
s^3 + 128.1 s^2 + 52.09 s

Closed loop
0 states have been removed from the model

      s^2 + 128.1 s + 52.09
--------------------------------
s^3 + 142.1 s^2 + 1509 s + 312.6

        gain: 0.167
        poles: [-130.551  -11.329   -0.211]
        zeros: [-127.657   -0.408]
Bode diagram
```



10^2
10^1
10^0
10^{-1}
10^{-2}
$|L|$
10^{-1}
10^0
10^1
10^2
10^3
ω (rad/sec)



−72.5
−75.0
−77.5
−80.0
−82.5
−85.0
−87.5
arg L (deg)
10^{-1}
10^0
10^1
10^2
10^3
ω (rad/sec)

4.3 Allosteric inhibition

Setting $\kappa_{re} = \kappa_{rc} = \kappa_{ra} = 1$ releases all feedback paths.

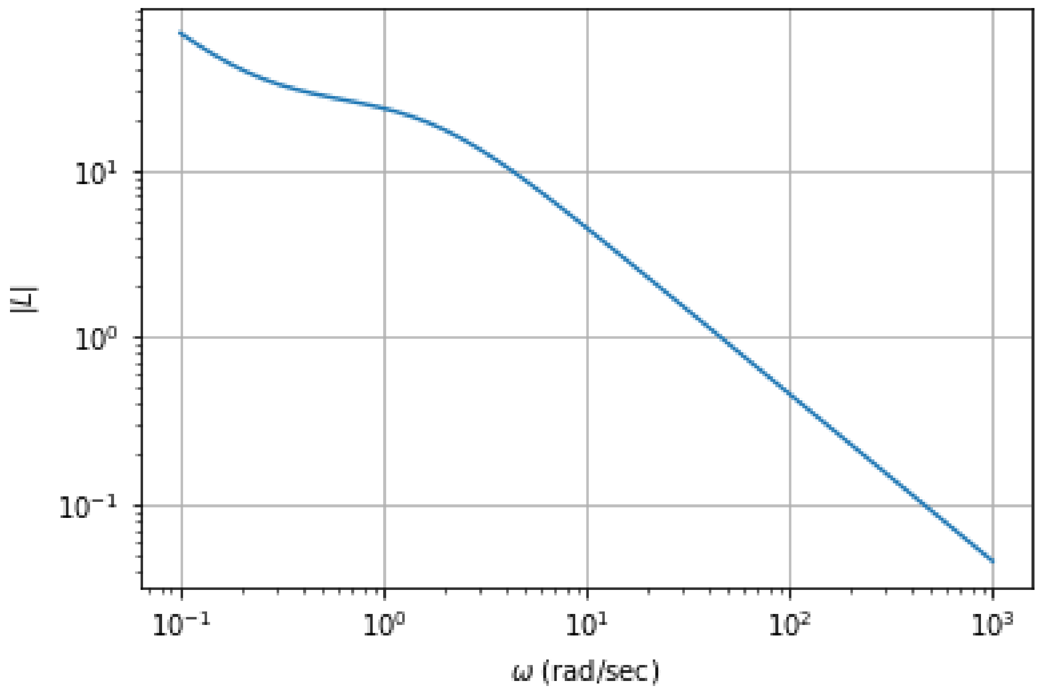
- All feedback paths are now in use.
- The main feedback path has a steady-state gain of about 5.
- The steady-state gains via v_{re} and v_{rc} are small - the effect of these paths is transient.
- The closed-loop system derived from L is the same as given above.

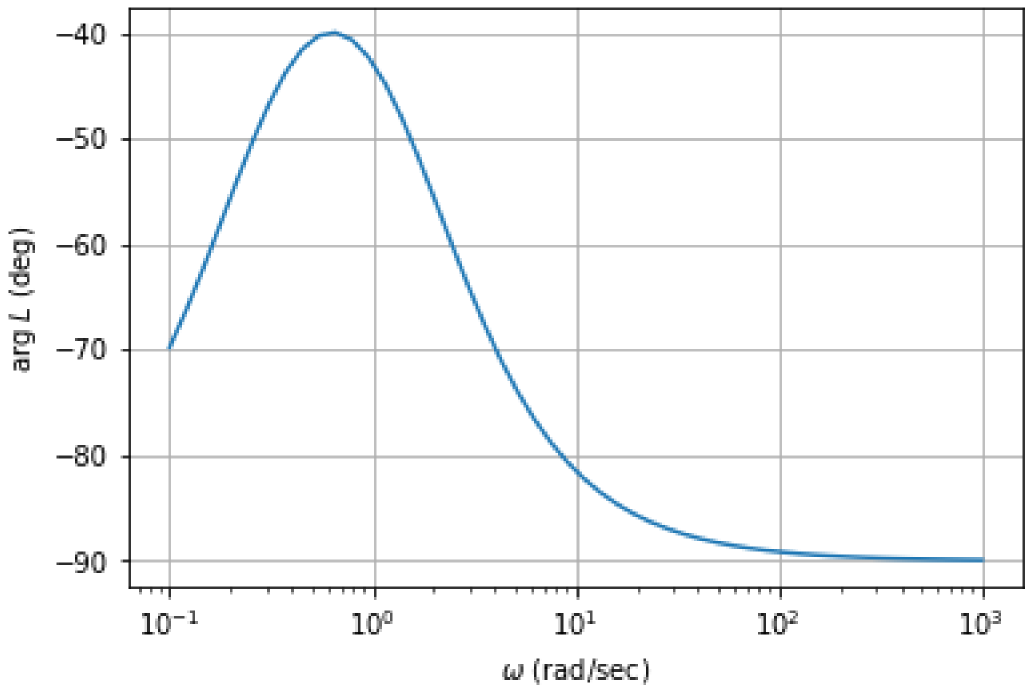
```
In [17]: ## Allosteric inhibition
         print('Allosteric inhibition')

         parameter['kappa_re'] = 1
         parameter['kappa_rc'] = 1
         parameter['kappa_ra'] = 1

         LoopGain(abg,chemostats,parameter,x_ss_ai,quiet=quiet)
```

```
Allosteric inhibition

Transfer function from x_B to v_r2
0 states have been removed from the model

-0.0003179 s^2 - 8.734 s - 910.2
--------------------------------
      s^2 + 105.5 s + 180.5

        gain: -5.042
        poles: [-103.751   -1.74 ]
        zeros: [-27366.453   -104.613]

Transfer function from x_B to v_r3
2 states have been removed from the model

1
-
1

        gain: 1.000
        poles: []
        zeros: []

Transfer function from x_B to v_rc
0 states have been removed from the model

8.704 s^2 + 903 s - 12.8
------------------------
  s^2 + 105.5 s + 180.5
```

```
        gain: -0.071
        poles: [-103.751   -1.74 ]
        zeros: [-1.038e+02  1.418e-02]

Transfer function from x_B to v_re
0 states have been removed from the model

-0.2476 s^2 - 25.69 s - 12.8
----------------------------
    s^2 + 105.5 s + 180.5

        gain: -0.071
        poles: [-103.751   -1.74 ]
        zeros: [-103.248   -0.501]

Relevant reactions: ['r2', 'r3', 'rc', 're']
Net feedback
5 states have been removed from the model

45.76 s + 10.51
---------------
    s + 1.74

        gain: 6.042
        poles: [-1.74]
        zeros: [-0.23]
Forward gain to B

1
-
s

        gain:   inf
        poles: [0.]
        zeros: []
Loop gain L

45.76 s + 10.51
---------------
  s^2 + 1.74 s

Closed loop
0 states have been removed from the model

      s + 1.74
--------------------
s^2 + 47.5 s + 10.51
```

```
        gain: 0.166
        poles: [-47.274  -0.222]
        zeros: [-1.74]
Bode diagram
```





5 Discussion

- A novel approach to determining loop-gains from bond graphs of biomolecular systems is given
- An example, enzyme catalysed reaction with allosteric inhibition, illustrates the approach
- In this simple case, the product x_B and the control signal v_2 are collocated; this would not generally be the case.
- Because of the collocation, the phase lag of the loop-gain is less that 90° (check this) thus there are no stability issues on closing the loop.
- Systems where the product is at the end of a chain of reactions are more problematic from the control point of view.
- There can be numerical issues with manipulating transfer functions. Minreal (minimum realisation) has been used here with a large tolerance to remove appoximate pole-zero cancellations. Balred (Balanced reduced order model) could also be useful here.
- Setting chemostatEMCM = False in the preamble shows the case where these species are not fixed.
- it would be interesting to apply this approach to the metabolic model of (Cloutier and Wellstead, 2010).

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