Sodium Glucose Symporter

Peter Gawthrop (peter.gawthrop@unimelb.edu au)

September 7, 2020

Contents

Note: This example is discussed in detail by (Gawthrop and Pan, 2020) available here.

Note: this is the SGLT.ipynb notebook. The PDF version "Sodium Glucose Symporter" is available here.

1 Introduction

The Sodium-Glucose Transport Protein 1 (SGLT1) (also known as the Na^+-glucose symporter (Keener and Sneyd, 2009, § 2.4.2)) was studied experimentally by Parent et al. (1992a) and explained by a biophysical model (Parent et al., 1992b); further experiments and modelling were conducted by Chen et al. (1995). Eskandari et al. (2005) examined the kinetics of the reverse mode using similar experiments and analysis to Parent et al. (1992a,b) but with reverse transport and currents.

This note looks at a bond graph based model of SGLT1 based on the model of Eskandari et al. (2005).

The model of Figure 6B of Eskandari et al. (2005) is based on the six-state biomolecular cycle of Figure 2 of Parent et al. (1992b). When operating normally, sugar is transported from the outside to the inside of the membrane driven against a possibly adverse gradient by the concentration gradient of Na^+.

A similar situation is analysed in §~1.1 of the book by Hill (1989) and the corresponding bond graph of the biomolecular cycle is described by Gawthrop and Crampin (2017).

```
In [1]: ## Some useful imports
        import BondGraphTools as bgt
        import numpy as np
        import sympy as sp
        import matplotlib.pyplot as plt

        ## Stoichiometric analysis
        import stoich as st

        ## SVG
        import svgBondGraph as sbg

        ## Display (eg disp.SVG(), disp.
        import IPython.display as disp

        quiet = True

        ## Data file
        import json
```

```
In /home/peterg/.local/lib/python3.6/site-packages/matplotlib/mpl-data/stylelib/_classic_test.mp
The text.latex.unicode rcparam was deprecated in Matplotlib 3.0 and will be removed in 3.2.
In /home/peterg/.local/lib/python3.6/site-packages/matplotlib/mpl-data/stylelib/_classic_test.mp
The savefig.frameon rcparam was deprecated in Matplotlib 3.1 and will be removed in 3.3.
In /home/peterg/.local/lib/python3.6/site-packages/matplotlib/mpl-data/stylelib/_classic_test.mp
The pgf.debug rcparam was deprecated in Matplotlib 3.0 and will be removed in 3.2.
In /home/peterg/.local/lib/python3.6/site-packages/matplotlib/mpl-data/stylelib/_classic_test.mp
```

```
The verbose.level rcparam was deprecated in Matplotlib 3.1 and will be removed in 3.3.
In /home/peterg/.local/lib/python3.6/site-packages/matplotlib/mpl-data/stylelib/_classic_test.mp
The verbose.fileo rcparam was deprecated in Matplotlib 3.1 and will be removed in 3.3.
```

In [2]:
```
## Load data from Eskandari et. al. Fig 3A
## Digitised using  https://apps.automeris.io/wpd/

def loadData():

    with open('DATA/SGLT_data.json') as f:
        Dict = json.load(f)

    List = Dict['datasetColl'][0]['data']

    X = []
    Y = []
    for item in List:
        xy = item['value']
        X.append(xy[0])
        Y.append(xy[1])

    return X,Y

print(loadData())
```

```
([-149.08132530120483, -128.50492880613362, -108.26396495071195, -88.92935377875138, -68.9204545
```

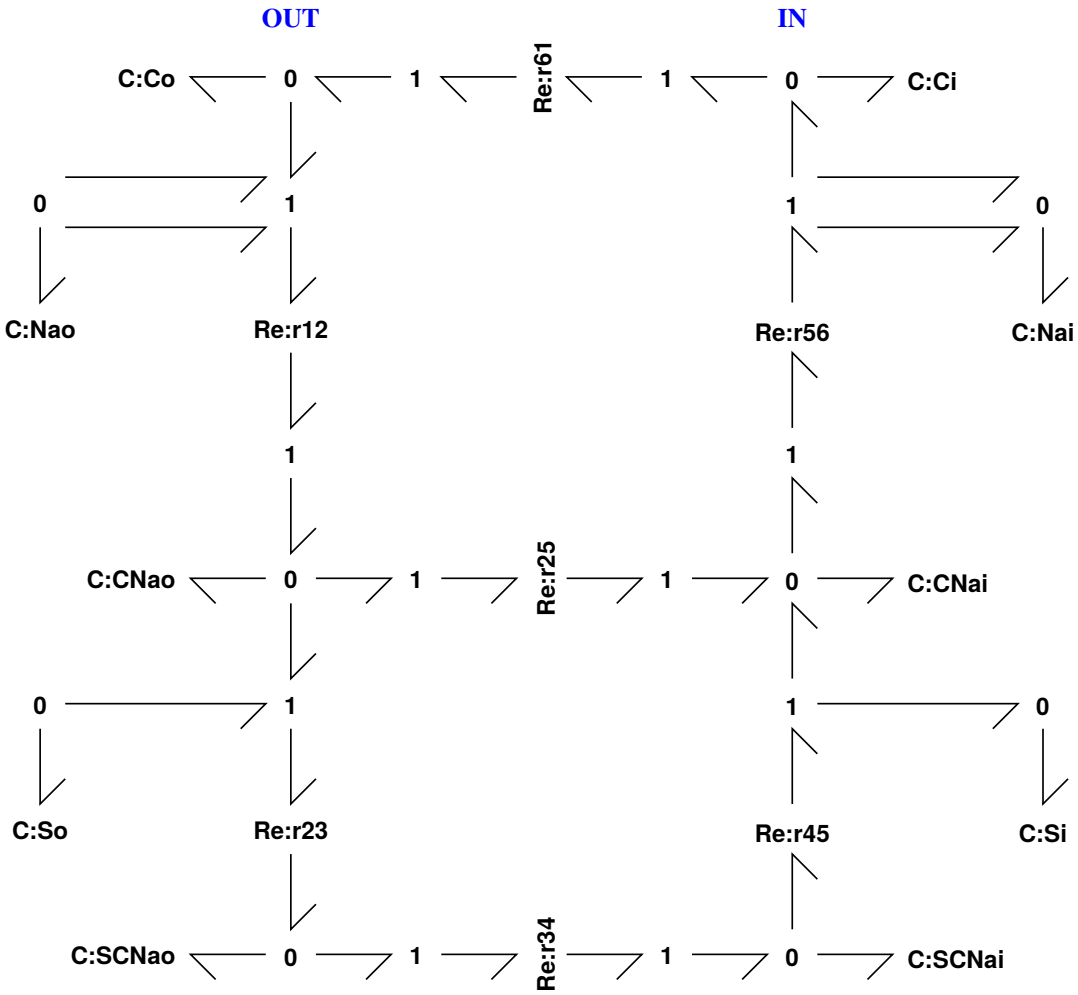
2 Sodium-Glucose Symporter - zero membrane potential.

This non-electrogenic version is used to compute species and reaction parameters from the published model values.

2.1 Bond graph

In [3]:
```
## Sodium-Glucose tranporter - no E
sbg.model('SGLT_abg.svg')
import SGLT_abg
disp.SVG('SGLT_abg.svg')
```

Out[3]:



2.2 Stoichiometry

```
In [4]: ## Stoichiometry
        s0 = st.stoich(SGLT_abg.model(),quiet=quiet)
        chemostats = ['Nai','Nao','Si','So']
        sc0 = st.statify(s0,chemostats=chemostats)
        #print(s['species'])
        #disp.Latex(st.sprint(s0,'K'))
        #print(st.sprints(s))
```

2.3 Convert parameters

The model of Eskandari et al. (2005) is based on rate constants. The following code converts this into the parameters required for the bond graph model.

```
In [5]: def Keq2K(K_eq,N,K,tol=1e-6):
            ## Compute BG C parameters K_c from equilibrium constants K_eq.
```

```
        ## NB K_eq must be thremodynamically consistent.

        logK_eq = np.log(K_eq)
        #print(K_eq)
        #print(logK_eq)

        if len(K) is not 0:
            ##First check that Keq is thermodynamically consistent.
            check = np.linalg.norm(K.T*logK_eq)/np.linalg.norm(logK_eq)
            print(check)

        ## Transformation of mu to affinities
        NN = -N.T

        ## Pseudo inverse
        pNN = np.linalg.pinv(NN)

        ## BG C constants
        K_c = np.exp(pNN@logK_eq)

        return K_c
```

In [6]:
```
## Set non-unit parameters using data from EskWriLoo05
def setPar(s,tol=1e-6):

    ## Extract stoichiometry
    N = s['N']
    Nf = s['Nf']
    Nr = s['Nr']
    K = s['K']

    n_V = s['n_V']


    ## Rate constants from Fig 6.
    kf = {}
    kr = {}

    ## Rate constants from Fig 6.
    kf['r12'] = 8e4;
    kr['r12'] = 500;

    kf['r23'] = 1e5;
    kr['r23'] = 20;

    kf['r34'] = 50;
    kr['r34'] = 50;
```

```
    kf['r45'] = 800;
    kr['r45'] = 12190;

    kf['r56'] = 10;
    kr['r56'] = 4500;

    kf['r61'] = 3;
    kr['r61'] = 350;

    kf['r25'] = 0.3;
    kr['r25'] = 9.1e-4;

    ## Equilibrium constants.
    K_eq = np.zeros(n_V)
    k_f = np.zeros(n_V)
    k_r = np.zeros(n_V)
    for i,reac in enumerate(s['reaction']):
        K_eq[i] = kf[reac]/kr[reac]
        k_f[i] = kf[reac]
        k_r[i] = kr[reac]

    ## Compute Ce constants from equilibrium constants
    K_c = Keq2K(K_eq,N,K)

#     print(K_eq)
#     print(s['n_X'], K_c.shape)

    # Forward rates induced by Cs
    k_f0 = np.exp(Nf.T@np.log(K_c))

    ## Rate constants kappa (Amps)
    kappa = (k_f/k_f0)*st.F()

    ## Sanity check
    k_r0 = np.exp(Nr.T@np.log(K_c))
    kappa_r = (k_r/k_r0)*st.F()
    check = np.linalg.norm(kappa-kappa_r)

    if check>tol:
        print(f'Error in kappa: {check:.2}')


    ## Parameters
    parameter = {}

    ## Ce constants
    for i,spec in enumerate(s['species']):
        print(f'K_{spec} = {K_c[i]:.4}')
```

```
                parameter['K_'+spec] = K_c[i]

            ## Re constants
            for i,reac in enumerate(s['reaction']):
                print(f'{reac} K_eq = {K_eq[i]:.4f}; kappa = {kappa[i]:.4f}')
                parameter['kappa_'+reac] = kappa[i]

            return parameter

        par = setPar(s0)
        #print(par)
```

```
Error in kappa: 1.2e-05
K_CNai = 0.149
K_CNao = 49.12
K_Ci = 0.3457
K_Co = 40.33
K_Nai = 13.93
K_Nao = 13.96
K_SCNai = 0.099
K_SCNao = 0.099
K_Si = 10.12
K_So = 10.08
r12 K_eq = 160.0000; kappa = 982183.7246
r23 K_eq = 5000.0000; kappa = 19492291.8173
r25 K_eq = 329.6703; kappa = 589.3102
r34 K_eq = 1.0000; kappa = 48730729.5432
r45 K_eq = 0.0656; kappa = 779691672.6910
r56 K_eq = 0.0022; kappa = 6475936.6454
r61 K_eq = 0.0086; kappa = 837303.6199
```

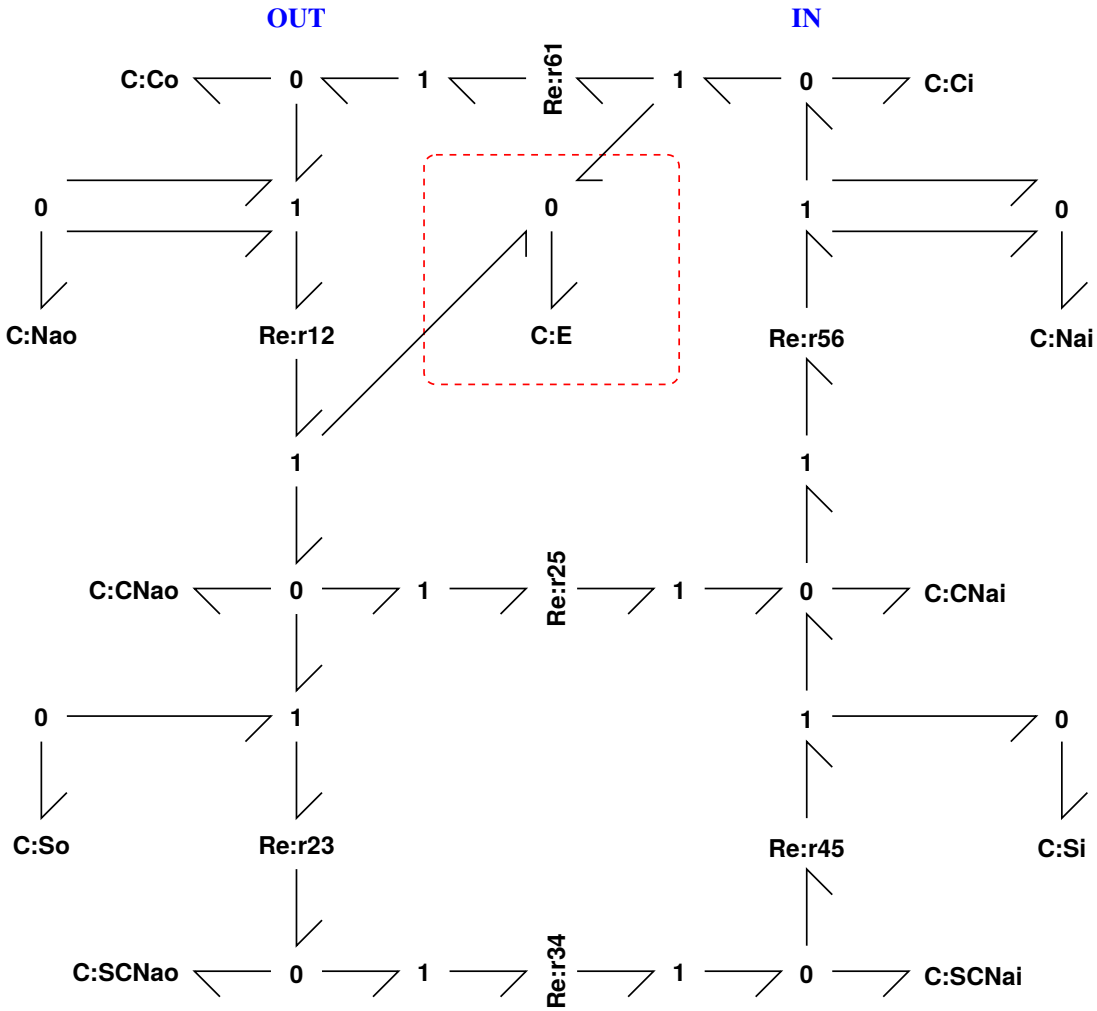
3 Electrogenic Sodium-Glucose Symporter

3.1 Bond graph

The component C:E is added to express the effect of the charged Na^+ ion crossing the membrane.

In [7]:
```
## Sodium-Glucose tranporter - electrogenic
sbg.model('ESGLT_abg.svg')
import ESGLT_abg
disp.SVG('ESGLT_abg.svg')
```

Out[7]:



3.2 Stoichiometry

```
In [8]: ## Stoichiometry
        s = st.stoich(ESGLT_abg.model(),linear=['E'], quiet=quiet)
        chemostats = ['Nai','Nao','Si','So','E']
        sc = st.statify(s,chemostats=chemostats)

        disp.Latex(st.sprint(sc,'K'))
```

```
K:
 [[ 0  1]
 [ 1  0]
 [-1  1]
 [ 1  0]
 [ 1  0]
 [ 0  1]
```

```
 [ 0  1]]
```

Out[8]: <IPython.core.display.Latex object>

3.3 Reactions and flows

In [9]:
```
## Reactions
disp.Latex(st.sprintrl(s,chemformula=True,all=True))
```

Out[9]:

$$\mathrm{Co} + 2\,\mathrm{Nao} \overset{r_{12}}{\rightleftharpoons} \mathrm{CNao} + \mathrm{E} \tag{1}$$
$$\mathrm{CNao} + \mathrm{So} \overset{r_{23}}{\rightleftharpoons} \mathrm{SCNao} \tag{2}$$
$$\mathrm{CNao} \overset{r_{25}}{\rightleftharpoons} \mathrm{CNai} \tag{3}$$
$$\mathrm{SCNao} \overset{r_{34}}{\rightleftharpoons} \mathrm{SCNai} \tag{4}$$
$$\mathrm{SCNai} \overset{r_{45}}{\rightleftharpoons} \mathrm{CNai} + \mathrm{Si} \tag{5}$$
$$\mathrm{CNai} \overset{r_{56}}{\rightleftharpoons} \mathrm{Ci} + 2\,\mathrm{Nai} \tag{6}$$
$$\mathrm{Ci} \overset{r_{61}}{\rightleftharpoons} \mathrm{Co} \tag{7}$$

In [10]:
```
## Flows
disp.Latex(st.sprintvl(s))
```

Out[10]:

$$v_{r12} = \kappa_{r12}\left(-K_{CNao}x_{CNao}e^{\frac{K_E x_E}{V_N}} + K_{Co}K_{Nao}^2 x_{Co}x_{Nao}^2\right) \tag{8}$$
$$v_{r23} = \kappa_{r23}\left(K_{CNao}K_{So}x_{CNao}x_{So} - K_{SCNao}x_{SCNao}\right) \tag{9}$$
$$v_{r25} = \kappa_{r25}\left(-K_{CNai}x_{CNai} + K_{CNao}x_{CNao}\right) \tag{10}$$
$$v_{r34} = \kappa_{r34}\left(-K_{SCNai}x_{SCNai} + K_{SCNao}x_{SCNao}\right) \tag{11}$$
$$v_{r45} = \kappa_{r45}\left(-K_{CNai}K_{Si}x_{CNai}x_{Si} + K_{SCNai}x_{SCNai}\right) \tag{12}$$
$$v_{r56} = \kappa_{r56}\left(K_{CNai}x_{CNai} - K_{Ci}K_{Nai}^2 x_{Ci}x_{Nai}^2\right) \tag{13}$$
$$v_{r61} = \kappa_{r61}\left(K_{Ci}x_{Ci}e^{-\frac{K_E x_E}{V_N}} - K_{Co}x_{Co}\right) \tag{14}$$

3.4 Sdet up initial conditions for simulation

In [11]:
```
def setX(s):

    sp = s['species']
    X0 = np.zeros(s['n_X'])
    X0[sp.index('So')] = 1e-6
    X0[sp.index('Si')] = 1e-3
```

```
        X0[sp.index('Nao')] = 1e-2
        X0[sp.index('Nai')] = 0.5

    #     X0 *= st.F()

        ## Normalised value
        C_T = 1
        others = ['Co','CNao','SCNao','Ci','CNai','SCNai']
        for spec in others:
            X0[sp.index(spec)] = C_T/len(others)

        #N_C = 3e6
        N_C = 7.5e7
        N_avo = 6.022e23
        C_T_0 = N_C/N_avo

        I_0_pA = 1e12*C_T_0/C_T

        print(f'N_C = {N_C}; i_0 = {I_0_pA}pA')

        #X0 *= st.F()

        return X0,I_0_pA

    #print(setX(s))
```

4 Comparison with experimental data

In [12]:
```
    ## Vary E
    E0 = -170/1000
    E1 = 50/1000
    #E1 = 200/1000
    X_chemo = {'E':str(E0)}
    ## Simulation
    t = np.linspace(0,1e3,100)
    parameter = setPar(s0)
    X0,I_0_pA = setX(s)
    dat = st.sim(s,sc=sc,t=t,parameter=parameter,X_chemo=X_chemo,X0=X0)

    ## Extract data
    spec = s['species']
    reac = s['reaction']
    X_ss = dat['X'][-1,:]
    print(X_ss[spec.index('E')])


    x_E = f'{E0} + {(E1-E0)/max(t)}*t'
```

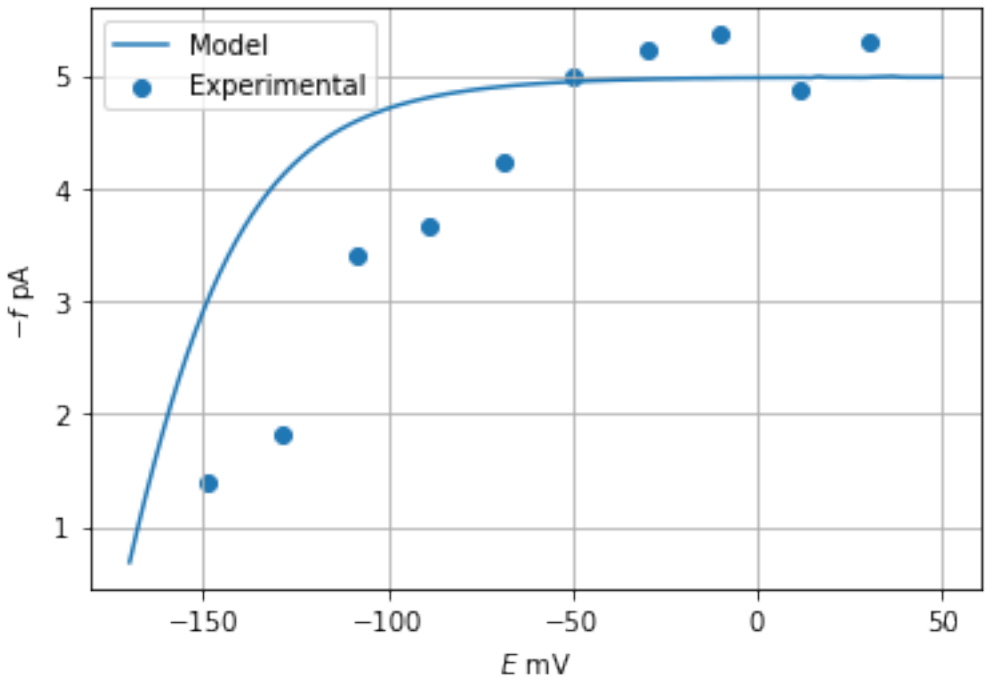
```
        print(x_E)
        X_chemo = {'E':x_E}

        dat = st.sim(s,sc=sc,t=t,parameter=parameter,X0=X_ss,X_chemo=X_chemo)
        f_E = dat['dX'][:,spec.index('E')]
        E = dat['X'][:,spec.index('E')]

        print(E[0],E[-1])

        X,Y = loadData()
        plt.plot(1000*E,-f_E*I_0_pA, label='Model')
        plt.scatter(X,Y,label='Experimental')
        plt.legend()
        plt.grid()
        plt.xlabel('$E$ mV')
        plt.ylabel('$-f$ pA')
        plt.savefig('Figs/sglt.pdf')
        plt.show()
```

```
Error in kappa: 1.2e-05
K_CNai = 0.149
K_CNao = 49.12
K_Ci = 0.3457
K_Co = 40.33
K_Nai = 13.93
K_Nao = 13.96
K_SCNai = 0.099
K_SCNao = 0.099
K_Si = 10.12
K_So = 10.08
r12 K_eq = 160.0000; kappa = 982183.7246
r23 K_eq = 5000.0000; kappa = 19492291.8173
r25 K_eq = 329.6703; kappa = 589.3102
r34 K_eq = 1.0000; kappa = 48730729.5432
r45 K_eq = 0.0656; kappa = 779691672.6910
r56 K_eq = 0.0022; kappa = 6475936.6454
r61 K_eq = 0.0086; kappa = 837303.6199
N_C = 75000000.0; i_0 = 0.00012454334108269677pA
-0.17
-0.17 + 0.00022000000000000003*t
-0.17 0.05000000000000002
```



References

Peter J. Gawthrop and Michael Pan. Network thermodynamical modelling of bioelectrical systems: A bond graph approach. Available at arXiv:2009.02217, 2020.

James P Keener and James Sneyd. *Mathematical Physiology: I: Cellular Physiology*, volume 1. Springer, New York, 2nd edition, 2009.

Lucie Parent, Stéphane Supplisson, Donald D. F. Loo, and Ernest M. Wright. Electrogenic properties of the cloned Na+/glucose cotransporter: I. voltage-clamp studies. *The Journal of Membrane Biology*, 125(1):49–62, 1992a. ISSN 1432-1424. doi:10.1007/BF00235797.

Lucie Parent, Stéphane Supplisson, Donald D. F. Loo, and Ernest M. Wright. Electrogenic properties of the cloned Na+/glucose cotransporter: II. a transport model under nonrapid equilibrium conditions. *The Journal of Membrane Biology*, 125(1):63–79, 1992b. ISSN 1432-1424. doi:10.1007/BF00235798.

Xing-Zhen Chen, Michael J Coady, Francis Jackson, Alfred Berteloot, and Jean-Yves Lapointe. Thermodynamic determination of the Na+: glucose coupling ratio for the human SGLT1 cotransporter. *Biophysical Journal*, 69(6):2405, 1995. doi:10.1016/S0006-3495(95)80110-4.

S. Eskandari, E. M. Wright, and D. D. F. Loo. Kinetics of the Reverse Mode of the Na+/Glucose Cotransporter. *J Membr Biol*, 204(1):23–32, Mar 2005. ISSN 0022-2631. doi:10.1007/s00232-005-0743-x. 16007500[pmid].

Terrell L Hill. *Free energy transduction and biochemical cycle kinetics*. Springer-Verlag, New York, 1989.

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.