

Simulations of a two-component system (*E.coli*)

Trial 1:

```
#!/usr/bin/env python3
# -*- coding: utf-8 -*-
"""
Created on Tue Nov 28 2024
Modified for the PhoQ-PhoP system

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"""

import numpy as np
import matplotlib.pyplot as plt
from scipy.integrate import odeint

####Full model#####

# Decide how to encode your system.
# A State vector [X] is conc. of all the components at a particular time.
# The order in which they are specified needs to remain fixed.
## Here, the system of PhoQ, PhoP, and related phosphotransfer reactions:
## PhoQ-P (Phosphorylated PhoQ)
## PhoP-P (Phosphorylated PhoP)
## MgrB (MgrB protein)
## PhoQ (Unphosphorylated PhoQ)
## PhoP (Unphosphorylated PhoP)
## X0 is the initial state/conditions
# Set initial conditions State vector is [PhoQ, PhoP, PhoQ-P, PhoP-P, MgrB]

init_state=np.array([20, 0, 0, 0, 0]) # Initial concentrations of PhoQ, PhoP,
PhoQ-P, PhoP-P, MgrB (μM)

# Declare your ODE model in the same order
## dX[0] = d[PhoQ]/dt, dX[1] = d[PhoP]/dt, dX[2] = d[PhoQ-P]/dt, dX[3] =
d[PhoP-P]/dt, dX[4] = d[MgrB]/dt
def diffEq(X, t):
    # generate a list to store derivatives
    dX = np.zeros(5)

    # PhoQ phosphorylation dynamics
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    dX[0] = -k1 * (X[0]) * (K1/(Ki + 20)) + k2 * (X[1]) + ksynQ * (X[2]/(Kprom1
+ X[2])) # d[PhoQ]/dt
    # PhoP phosphorylation dynamics
    dX[1] = k1 * (X[0]) * (K1/(Ki + 20)) - k2 * (X[1]) # d[PhoP]/dt
    # PhoQ-P dynamics
    dX[2] = -k3 * (X[1]) * (X[3]/(km + X[3])) - k5 * (X[0]) * (X[2]/(km2 +
X[2])) + k6 * (X[1]) * (X[3]) * (1/1+(X[4]/Ki2)) # d[PhoQ-P]/dt
    # PhoP-P dynamics
    dX[3] = -k3 * (X[1]) * (X[3]/(km + X[3])) + ksynP * (X[2]/(Kprom1 + X[2]))
+ k5 * (X[0]) * (X[2]/(km2 + X[2])) # d[PhoP-P]/dt
    # MgrB dynamics
    dX[4] = ksynM * (X[2]/(Kprom2 + X[2])) - kd * X[4] # d[MgrB]/dt

    return dX

#dX[0] = PhoQ
#dX[1] = PhoQ-P
#dX[2] = PhoP-P
#dX[3] = PhoP
#dX[4] = MgrB

# Assign parameter values based on the provided system
k1 = 12.5 #PhoQ* autophosphorylation rate (s^-1)
k2 = 0 #PhoQ-P autodephosphorylation rate (s^-1)
K1 = 5 #PhoQ-P to PhoP association rate - I have taken the same for the
dissociation rate (μM^-1 s^-1)
Ki = 10 #Inhibition rate constant of Mg2+ for PhoQ (μM)
ksynQ = 3.7*10**-2 #PhoP translation rate - will be same for PhoQ (s^-1)
ksynP = 3.7*10**-2 #PhoP translation rate (s^-1)
Kprom1 = 0.62 #Affinity of PhoP-P to PphoP Q (μM)
k3 = 3.6*10**0 #[PhoQ-P.PhoP] phosphotransfer rate (s^-1)
km = 2 #Michaelis Menten constant for interaction between PhoP-P and PhoQ (μM)
k5 = 1.56 #[PhoQ.PhoP-P] dephosphorylation rate (s^-1)
km2 = 5 #Michaelis Menten constant for interaction between PhoP-P and PhoP (μM)
ksynM = 2.3*10**-2 #MgrB translation rate (s^-1)
Kprom2 = 0.19 #Affinity of PhoP-P to PmgrB (μM)
Ki2 = 0.5 #Inhibition rate constant of MgrB for PhoP-P (μM)
k6 = 4.6*10**-3 #[PhoQ-P.PhoP] dissociation rate (s^-1)
kd = 0.83 #MgrB decay constant (s^-1)

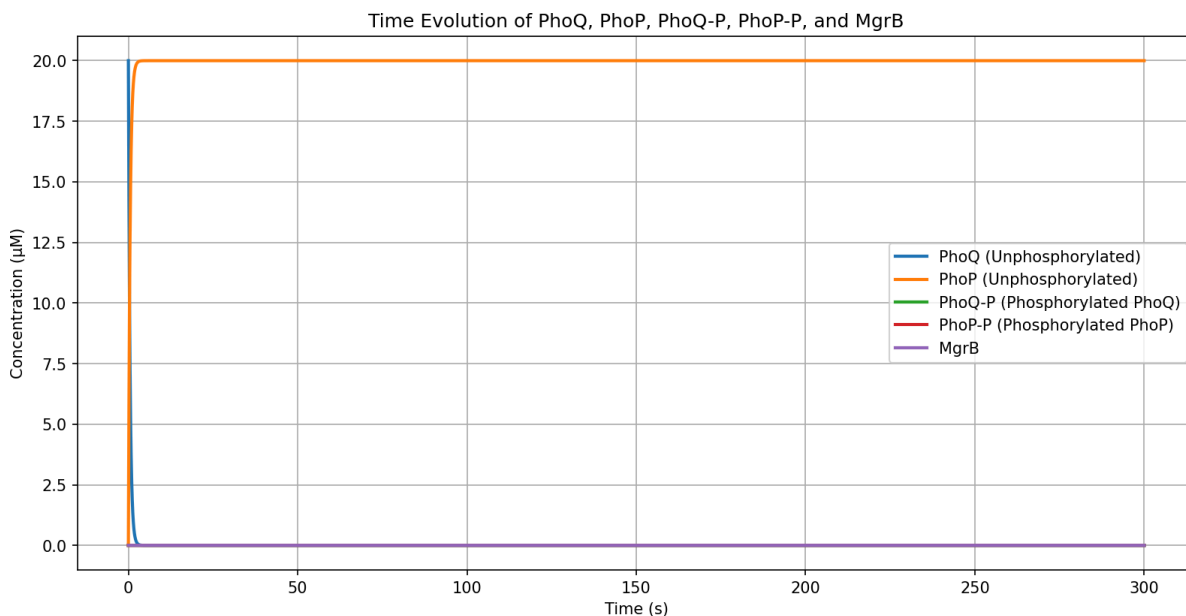
#set time_grid for simulation
t_min=0; t_max=300; dt=0.001
times=np.arange(t_min, t_max+dt, dt) #generate time-grid list

X=odeint(diffEq, init_state, times) #run simulation

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# Plot the simulation
plt.figure() # Generate figure
plt.plot(times, X[:, 0], label="PhoQ (Unphosphorylated)", linewidth=2)
plt.plot(times, X[:, 1], label="PhoP (Unphosphorylated)", linewidth=2)
plt.plot(times, X[:, 2], label="PhoQ-P (Phosphorylated PhoQ)", linewidth=2)
plt.plot(times, X[:, 3], label="PhoP-P (Phosphorylated PhoP)", linewidth=2)
plt.plot(times, X[:, 4], label="MgrB", linewidth=2)
plt.xlabel("Time (s)")
plt.ylabel("Concentration (μM)")
plt.legend()
plt.title("Time Evolution of PhoQ, PhoP, PhoQ-P, PhoP-P, and MgrB")
plt.grid(True)
plt.show()
```

Plot:



Got a very weird plot, which does not show the expected relation. I tried changing the values and parameters but still couldn't get the expected plot.

Trial 2:

Asked ChatGPT to help with manipulating my code to get the correct dynamics (based on a literature review) of the network:

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

```

from scipy.integrate import odeint

# Initial state: [PhoQ, PhoP, PhoQ-P, PhoP-P, MgrB, Mg2+]
init_state = np.array([20, 10, 0, 0, 0, 1.0]) # Initial concentrations (μM),
Mg2+ starts high (1.0)

# Modified ODE model
def diffEq(X, t):
    dX = np.zeros(6)

    PhoQ, PhoP, PhoQ_P, PhoP_P, MgrB, Mg2 = X # Unpack variables

    # Mg2+ decay over time (simulating environmental change)
    dX[5] = -0.01 * Mg2 # Linear decay

    # Mg2+ effects on PhoQ activity (phosphatase vs kinase)
    inhibition_factor = Mg2 / (Ki + Mg2) # High Mg2+ inhibits kinase activity

    # PhoQ dynamics
    dX[0] = -k1 * PhoQ * (1 - inhibition_factor) + k2 * PhoQ_P # Kinase vs
phosphatase

    # PhoP dynamics
    dX[1] = -k3 * PhoP * PhoQ_P + k4 * PhoP_P #
Phosphorylation/dephosphorylation

    # PhoQ-P dynamics
    dX[2] = k1 * PhoQ * (1 - inhibition_factor) - k2 * PhoQ_P # Kinase vs
phosphatase

    # PhoP-P dynamics
    dX[3] = k3 * PhoP * PhoQ_P - k4 * PhoP_P #
Phosphorylation/dephosphorylation

    # MgrB dynamics (regulated by PhoP-P)
    dX[4] = ksynM * PhoP_P / (Kprom2 + PhoP_P) - kd * MgrB # Production and
decay

    return dX

# Parameters
k1 = 1.0 # PhoQ kinase rate
k2 = 0.5 # PhoQ phosphatase rate
k3 = 1.5 # PhoP phosphorylation by PhoQ-P
k4 = 0.8 # PhoP-P dephosphorylation by PhoQ

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ksynM = 0.02 # MgrB synthesis rate
Kprom2 = 0.5 # PhoP-P activation threshold for MgrB
kd = 0.01 # MgrB decay rate
Ki = 0.5 # Mg2+ inhibition constant for PhoQ

# Time grid
t_min, t_max, dt = 0, 300, 0.1
times = np.arange(t_min, t_max + dt, dt)

# Solve ODE
X = odeint(diffEq, init_state, times)

# Plot results
plt.figure(figsize=(8, 6))
plt.plot(times, X[:, 0], label="PhoQ", linestyle="--", linewidth=2)
plt.plot(times, X[:, 1], label="PhoP", linestyle="--", linewidth=2)
plt.plot(times, X[:, 2], label="PhoQ-P (Kinase)", linestyle="-", linewidth=2)
plt.plot(times, X[:, 3], label="PhoP-P (Phosphorylated PhoP)", linestyle="-",
linewidth=2)
plt.plot(times, X[:, 4], label="MgrB", linestyle="-. ", linewidth=2)
plt.plot(times, X[:, 5], label="Mg2+", linestyle=":", linewidth=2)
plt.xlabel("Time (s)")
plt.ylabel("Concentration (μM)")
plt.legend()
plt.title("PhoQ-PhoP Induction Kinetics")
plt.grid(True)
plt.show()

```

Changes in code:

Addition of $dX[5]$ for Mg^{2+} Decay:

- Linear decay of Mg^{2+} ($dX[5] = -0.01 * Mg2$) was introduced to simulate the depletion of environmental Mg^{2+} over time. This reflects the biological condition of low Mg^{2+} inducing the PhoQ-PhoP system.

Mg^{2+} Inhibition Factor for Mg^{2+} -Dependent PhoQ Activity:

- Introduced $inhibition_factor = Mg2 / (Ki + Mg2)$ to model Mg^{2+} inhibition of PhoQ's kinase activity. As Mg^{2+} decreases, the inhibition lessens, and PhoQ's kinase activity increases. This adjustment aligns with the known behavior of PhoQ under varying Mg^{2+} levels.

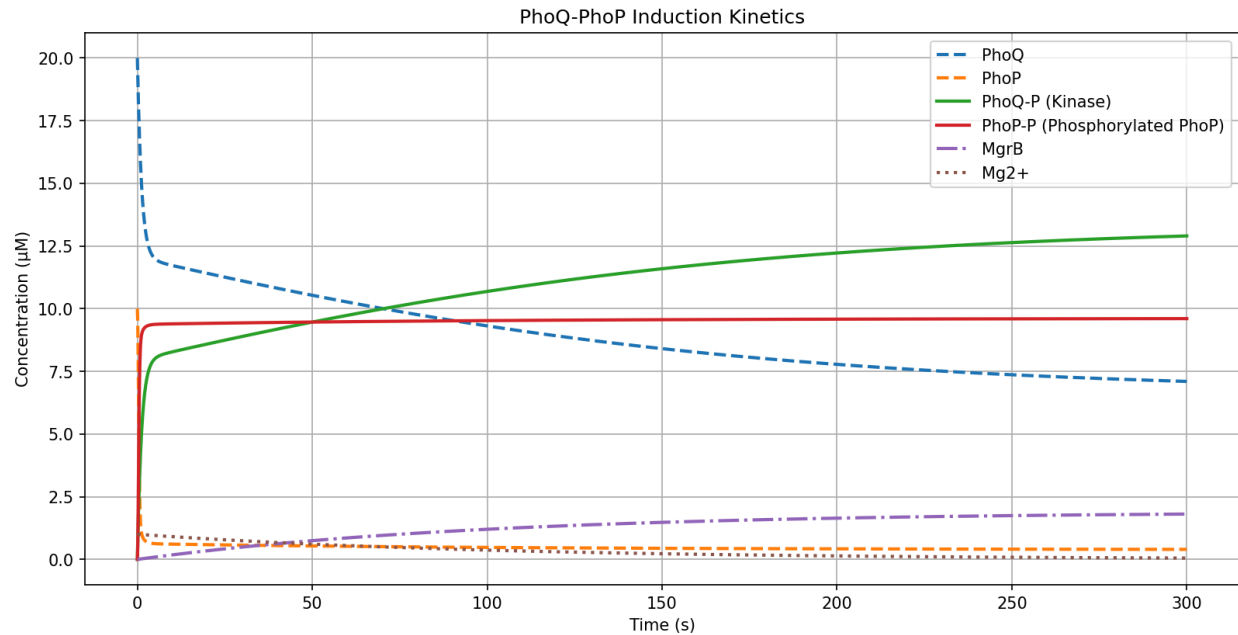
Modified PhoQ Dynamics:

- Updated $dX[0]$ and $dX[2]$ to incorporate inhibition_factor , balancing PhoQ's kinase and phosphatase activities. This allows PhoQ-P levels to rise under low Mg^{2+} conditions, matching the biological response.

Revised MgrB Dynamics:

- Adjusted $dX[4]$ to include PhoP-P activation using a Hill-type function ($\text{ksynM} * \text{PhoP_P} / (\text{Kprom2} + \text{PhoP_P})$) and a decay term ($-\text{kd} * \text{MgrB}$). This captures the production of MgrB as a feedback regulator controlled by PhoP-P.

Plot:



PhoQ and PhoQ-P Dynamics: The rapid decline of PhoQ and a steady rise in PhoQ-P are consistent with the activation of PhoQ's kinase activity under low Mg^{2+} conditions. This behavior aligns with PhoQ sensing environmental signals and transitioning to its active phosphorylated state.

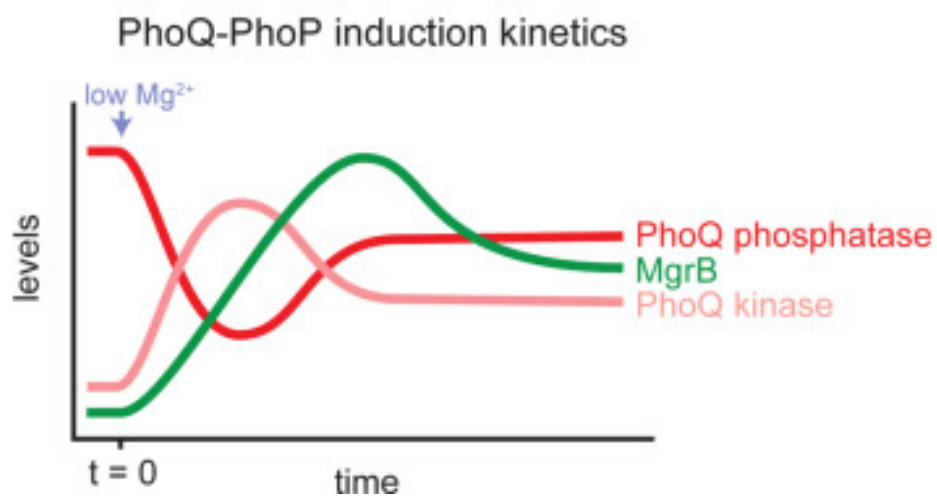
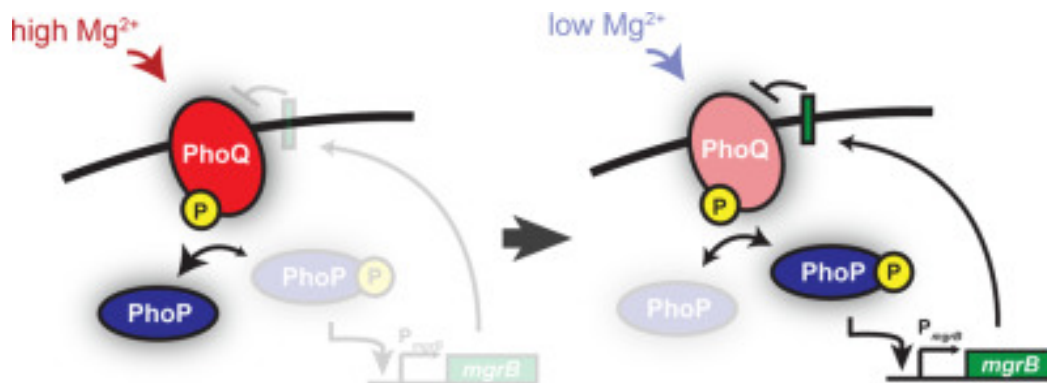
PhoP and PhoP-P Levels: The quick increase in PhoP-P indicates efficient phosphorylation by PhoQ-P. The relatively constant level of unphosphorylated PhoP suggests an adequate supply of substrate for PhoQ-P activity. This pattern aligns biologically with the role of PhoP-P in activating downstream gene expression.

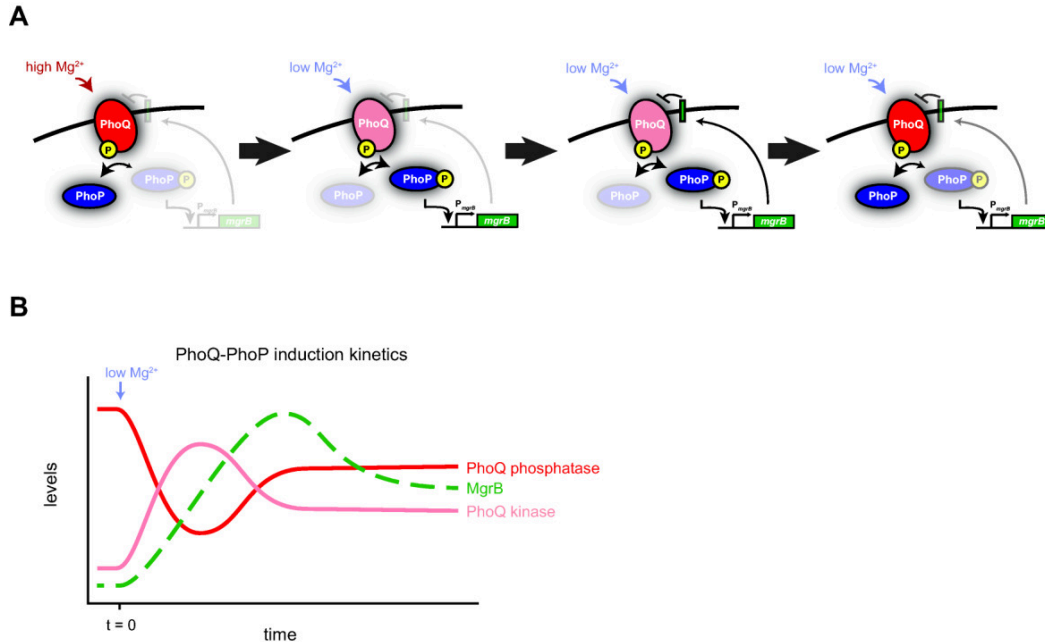
MgrB Dynamics: MgrB's delayed and gradual increase reflects its regulation by PhoP-P and subsequent production. This aligns with its role in providing feedback inhibition to PhoP-P production.

Mg²⁺ Levels: The linear decline of Mg²⁺ reflects environmental depletion, which triggers the PhoQ-PhoP system.

However, there are some mistakes in the plot, that is some of the values increasing/decreasing are very sudden instead of being gradual (like for PhoQ-P, PhoP-P, and PhoQ), the increase or decrease in this should be gradual.

Validation:





Example plot of the dynamics of certain components of the PhoQ-PhoP network in *E. coli*

Source:

<https://onlinelibrary.wiley.com/cms/asset/5ee1b9c4-30ea-47c4-b14e-e855c4d393e5/mmi13471-toc-0001-m.jpg>

The plot that I got from my simulation is different from the plot from the above paper.

For instance,

1. The Phosphatase levels decrease and then increase over time in the above plot. → Not present in my plot.
 2. The MgrB levels increase and then decrease a little and plateau. → In my plot it just shows that it increases over time (it could be because I have not added the decay constant in the new code).
 3. PhoQ kinase also increases and then reduces a little and plateau → In my plot it reduces over time.
- (This plot is just showing the induction of the PhoQ kinase by Mg^{2+} and doesn't include the conversion of the PhoQ to PhoQ-P.