# BT5240: Computational Systems Biology

Assignment 4 - Report

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BE21B038

1 Dynamic Modeling

a. During the production of acetate in E. coli it was observed that when extracellular acetate increases, the acetate flux in E. coli reverses, i.e, E. coli starts consuming acetate. This shift in metabolic activity is known as overflow metabolism. This mechanism is represented in the following diagram. The new kinetic model to explain this phenomenon has 2 compartments (cell and environment), 6 reactions and 6 metabolites. The table shows the various parameters associated with the kinetic model.
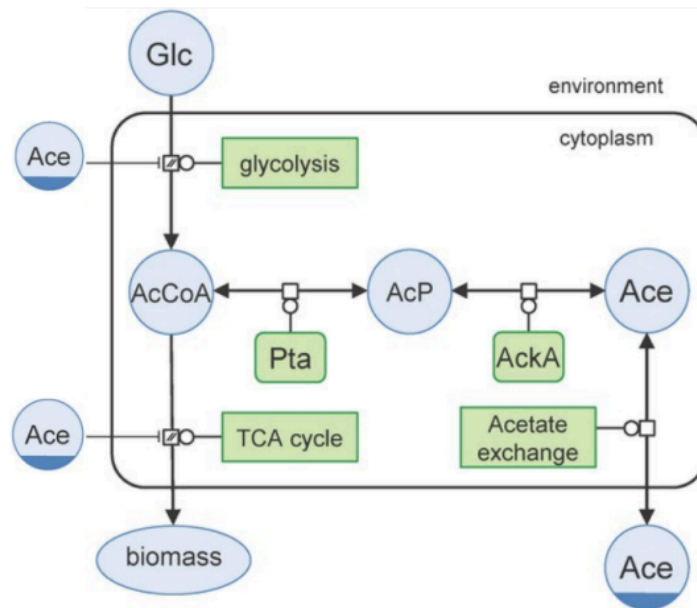
Parameter	Description
$v_{glycolysis}$	Glycolysis rate of reaction
v_{TCA_cycle}	Rate of reaction of TCA cycle
v_{AckA}	Rate of reaction of acetate kinase
v_{Pta}	Rate of reaction of Phosphotransacetylase
v_{feed}	Rate of reaction of glucose feed
$v_{Acetate\_exchange}$	Rate of reaction of acetate reaction.
AcP	Acetyl Phosphatase
AcCoA	Acetyl-coenzyme A

Taking the diagram as reference, write Differential equations for the above system for all the metabolites

b. If the glucose concentration in the model is given by the equation

$$G(t) = Go - (Bo / Y) . (e^{ut} - 1)$$

Where, Go and G(t) are the glucose concentration at time 0 and t. And Bo is the initial biomass concentration. μ is the growth rate per hour. Simulate the Glucose concentration if Go and Bo are 12mM and 0.1 gDW/L. μ is 0.35 h -1 and Y = 0.2 g/mM.L

Solution: a.

(i) Glc $\Rightarrow$ $\dfrac{d[A]}{dt} = -v_1 + v_5$ [since 1 is inhibited by E, those effects will also add to the equation if the type of inhibition is known]

(ii) Biomass $\Rightarrow$

$\dfrac{d[B]}{dt} = v_2$ [since 2 is inhibited by E, those effects will also add to the equation if the type of inhibition]

(iii) Ace - Cytoplasm $\Rightarrow$

$\dfrac{d[C]}{dt} = v_3 - v_6$ [considering $\rightarrow$ & $\downarrow$ as the +ve direction of reaction] for 3 & 6 respectively

(iv) AcCoA $\Rightarrow$

$\dfrac{d[D]}{dt} = v_1 - v_2 - v_4$ [considering $\rightarrow$ as the direction of reaction 4. Inhibition effects of E will play a role in 1 & 2]

(v) Ace - Environment $\Rightarrow$
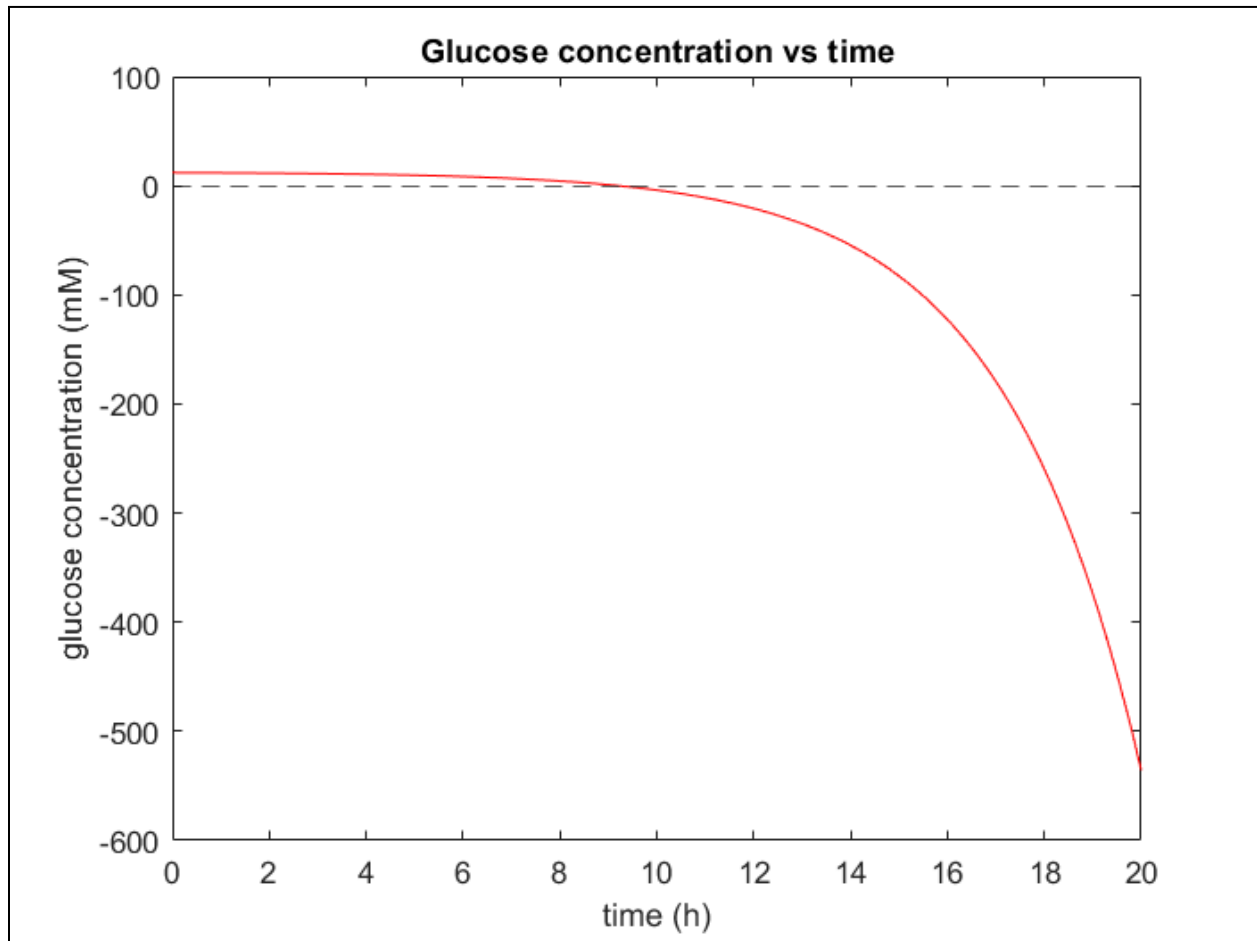
$\dfrac{d[E]}{dt} = v_6$ [considering $\downarrow$ as the +ve direction of reaction for 6]

(vi) AcP $\Rightarrow$

$\dfrac{d[F]}{dt} = v_4 - v_3$ [considering $\rightarrow$ as the +ve direction of reaction for 3 and 4]

b.

Plotting glucose concentration as a function of time following the given kinetics at the given parameters and initial conditions, we see that there is an exponential decrease in the concentration with increasing time. Negative glucose concentration after about 9 hours can be interpreted as glucose exit from the cell into the extracellular environment.

2 Dynamical Modeling of Gene Regulation

Various network motifs are commonly seen in Gene Regulatory Networks. These motifs can exhibit robust behaviors under appropriate conditions. One such interesting behavior is oscillations. It is seen that repressilators can often show oscillations. Examples of repressilator motifs are shown below.
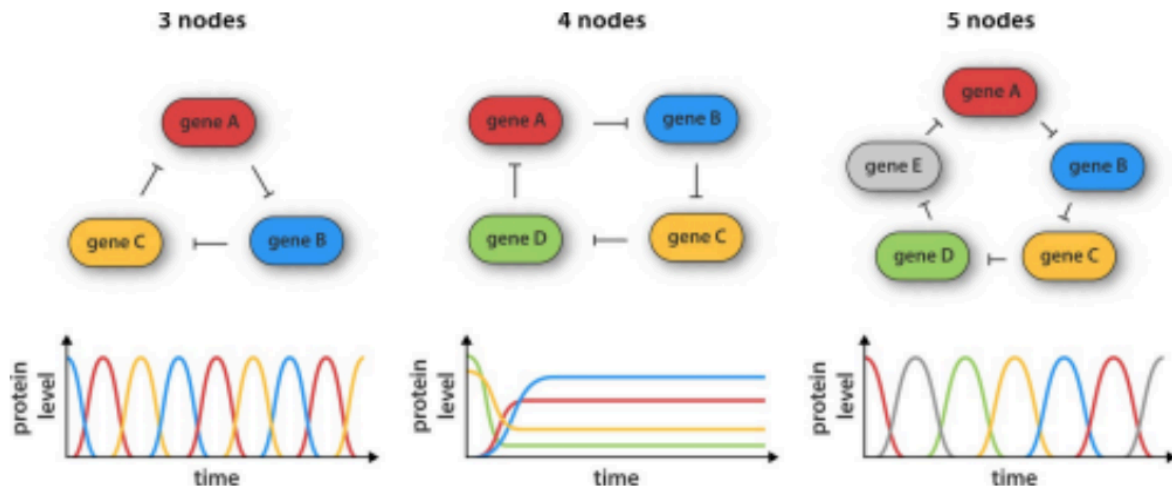
[Adopted from Rosier et al eLife 2015]

a. Simulate the three node repressilator using the parameters given above for 1000 time points. What behavior do you observe? Do you observe oscillations? If yes, is the amplitude sustained or decaying? Is the time period sustained or decaying?

b. Extend this to include four nodes. Modify the equations appropriately and simulate it for 1000 time points. What behavior do you observe? Do you observe oscillations? If yes, is the amplitude sustained or decaying? Is the time period sustained or decaying?

c. Further extend this for five nodes. Modify the equations appropriately and simulate it for 5000 time points. What behavior do you observe? Do you observe oscillations? If yes, is the amplitude sustained or decaying? Is the time period sustained or decaying?

Solution:

Given model equation as:

$$Hills(M) = \frac{\lambda M^n + M_0^n}{M^n + M_0^n}$$

parameters as:

```
g = 50;

k = 0.05;

lambda = 0.001;

M_0 = 10;

n = 2;
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initial conditions as:

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A_0 = 0.01;

B_0 = 10;

C_0 = 0.1;

D_0 = 10;

E_0 = 0.1;
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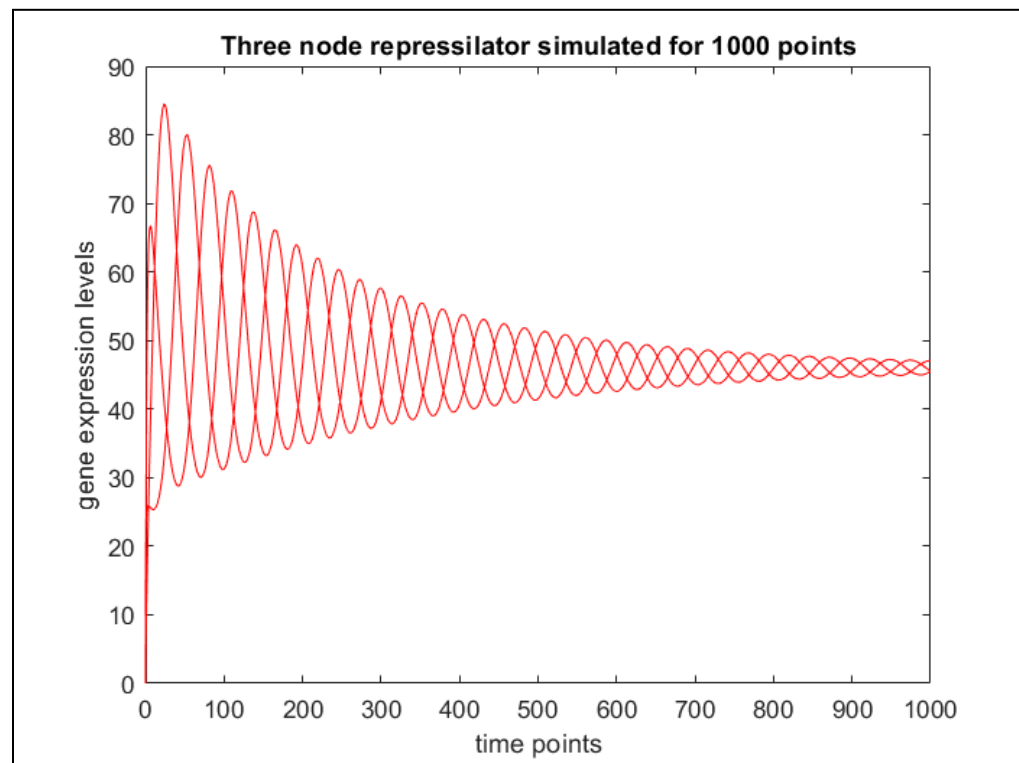
a. The system of equations for the three node repressilator is as follows:

```
dA/dt = g*hills(C) - k*A;

dB/dt = g*hills(A) - k*B;

dC/dt = g*hills(B) - k*C;
```

Plot:

Three node repressilator simulated for 1000 points

Observations:

- Oscillations have been observed
- Amplitude is decaying
- Time period is sustained

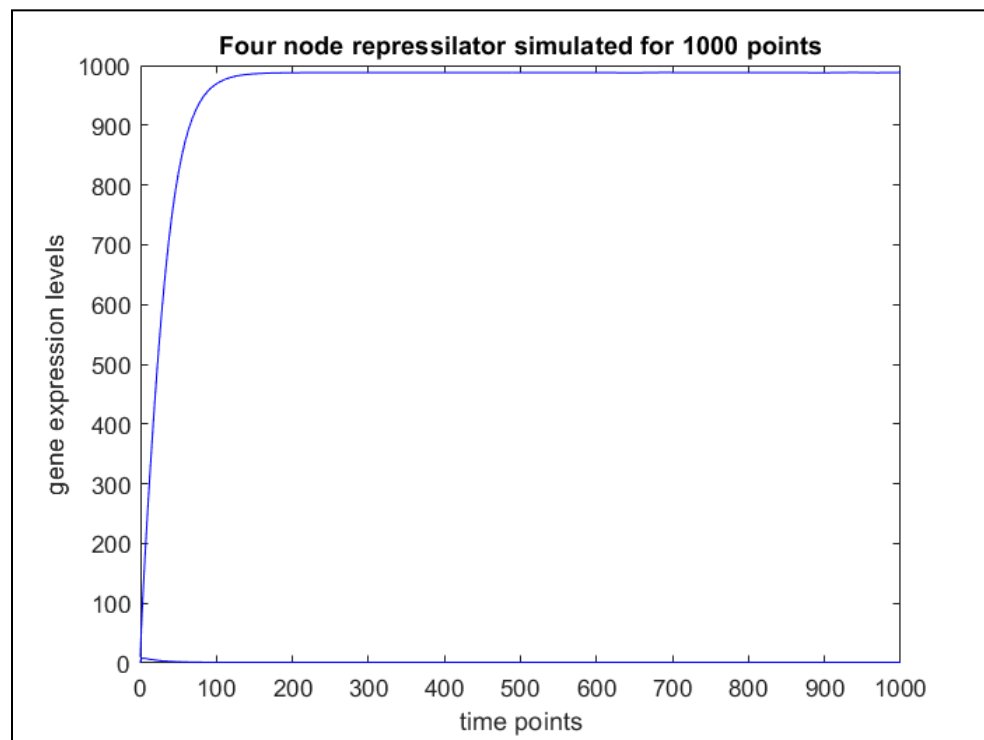b. The system of equations for the four node repressilator is as follows:

```
dA/dt = g*hills(D) - k*A;

dB/dt = g*hills(A) - k*B;

dC/dt = g*hills(B) - k*C;

dD/dt = g*hills(C) - k*D;
```

Plot:

Four node repressilator simulated for 1000 points

Observations:

- No oscillations have been observed
- The expression levels seem to stagnate after a short time

c. The system of equations for the five node repressilator is as follows:
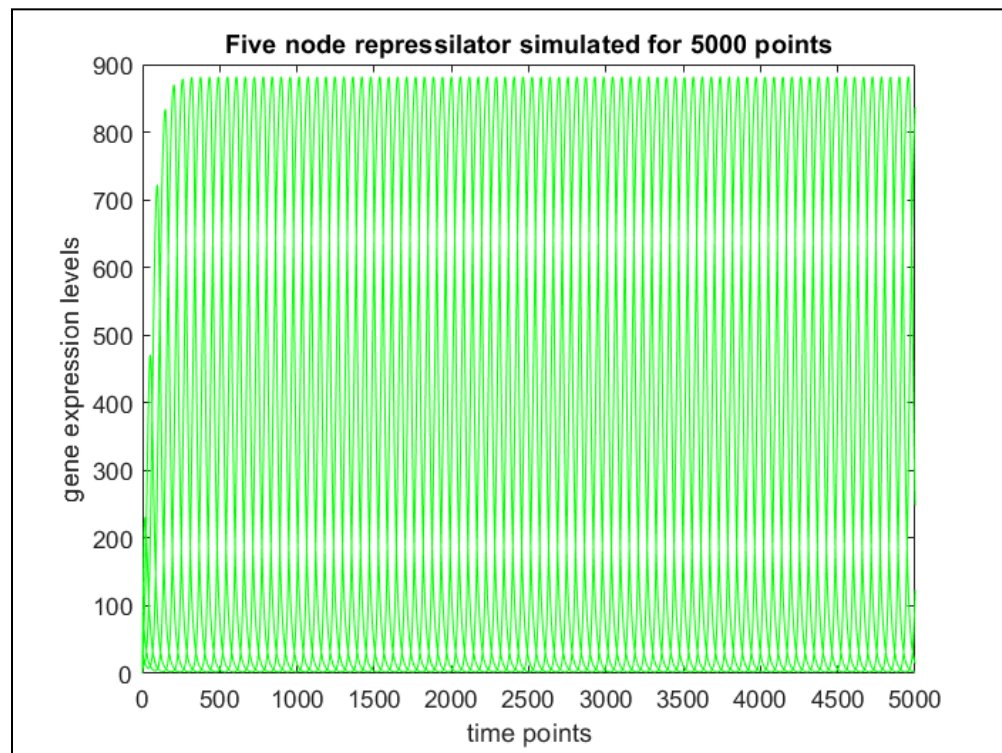
```
dA/dt = g*hills(E) - k*A;

dB/dt = g*hills(A) - k*B;

dC/dt = g*hills(B) - k*C;

dD/dt = g*hills(C) - k*D;

dE/dt = g*hills(D) - k*E;
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Plot:

Observations:

- Oscillations have been observed
- Initially, oscillations are increasing in amplitude, but quickly stagnate
- Time period is sustained