CHEME 7770 HW3

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1 1 part a

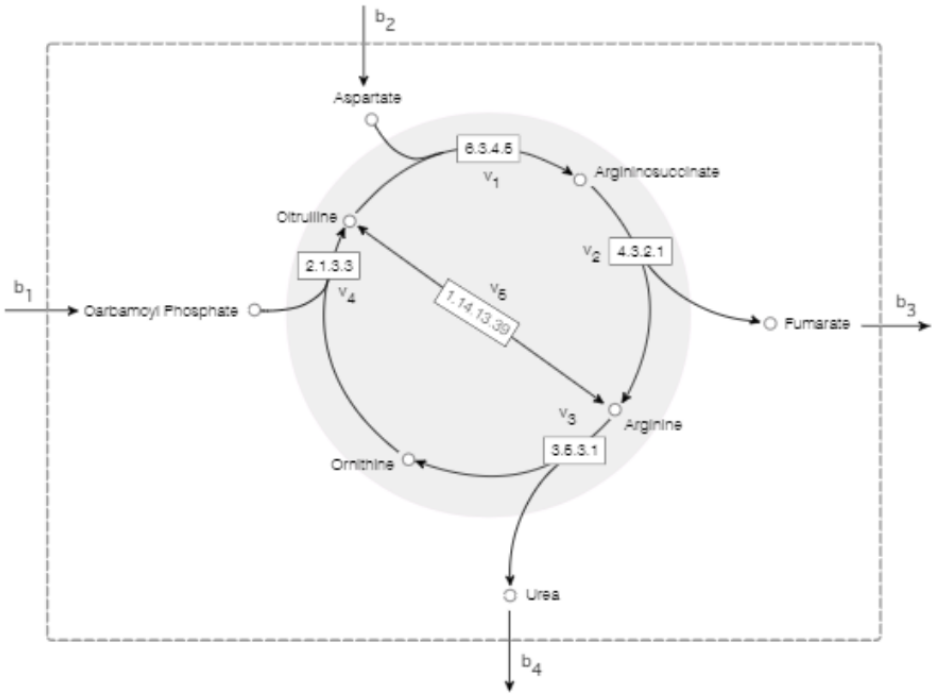

Figure 1: Schematic of the Urea cycle.

Figure 1: Schematic of the Arginine Biosynthesis Pathway

Below is the stoichimetric matrix for the arginine biosynthesis pathway where the rows represent each metabolite within the pathway. The stoichiometrix matrix below has the rows representing the following metabolites in the given order: aspartate, argininosuccinate, fumarate, arginine, urea, ornithine, caramoyl

phosphate, citrulline, ATP, AMP, PPi, H_2O, Pi, NADPH, H^+, O_2, $NADP^+$, and NO. Additionally v_{5f} represents the reaction from converting citrulline to arginine.

$$[S] = \begin{bmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & -2 & 2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1.5 & -1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1.5 & -1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2 & -2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1.5 & 1.5 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \end{bmatrix} \tag{1}$$

We assume that the change in metabolites with respect to time is 0 or that the two arrays, the stoichiometrix matrix and the flux vector (a column vector of all the reactions), multiplied together equals 0, as shown below where [S] represents the stoichiometrix matrix and [F] represents the flux vector. Given by the following vector.

$$[F] = \begin{bmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_{5f} \\ v_{5r} \\ b_1 \\ b_2 \\ b_3 \\ b_4 \\ b_5 \\ b_6 \\ b_7 \\ b_8 \\ b_9 \\ b_{10} \\ b_{11} \\ b_{12} \\ b_{13} \\ b_{14} \end{bmatrix} \tag{2}$$

$$\frac{dx_i}{dt} = 0 = [S] * [F] \tag{3}$$

2 1 part b

The atom matrix is shown below with the columns representing the metabolites in the same order as the rows of the Stoichiometrix matrix from part A.

$$[A] = \begin{bmatrix} 4 & 10 & 4 & 6 & 1 & 5 & 1 & 6 & 10 & 10 & 0 & 0 & 0 & 21 & 0 & 0 & 21 & 0 \\ 7 & 18 & 4 & 14 & 4 & 12 & 4 & 13 & 16 & 14 & 4 & 2 & 3 & 30 & 1 & 0 & 29 & 0 \\ 1 & 4 & 0 & 4 & 2 & 2 & 1 & 3 & 5 & 5 & 0 & 0 & 0 & 7 & 0 & 0 & 7 & 1 \\ 4 & 6 & 4 & 2 & 1 & 2 & 5 & 3 & 13 & 7 & 7 & 1 & 4 & 17 & 0 & 2 & 17 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 3 & 1 & 2 & 0 & 1 & 3 & 0 & 0 & 3 & 0 \end{bmatrix} \tag{4}$$

Multiplying the Atom Matrix by the Stoichiometrix Matrix should result in zeroes at least for the first six columns, representing v_1 through v_{5r}, to show that these reactions are balanced for carbon, hydrogen, oxygen, nitrogen, and phosphorous flux as shown by the Matrices.jl file.

3 1 part c

Constraining the fluxes and assigning a flux to be the objective function allows us to solve for fluxes within the system. Constraints of enzymatic reactions are shown below:

$$0 \leq v_j \leq V^o_{max,j}(\frac{e_j}{e^o_j})\theta_j f_j(m_1, m_2..., m_M, \kappa) \tag{5}$$

It is given that all enzymes are maximally active, the steady state enzyme concentration is given by .01 $\frac{\mu mol}{gDw}$, the maximum enzyme activity are all given from the problem set. The saturation of the enzymes are given by michaelis-menten kinetics. Steady state concentrations of reactants from enzymes were taken from the Park et al paper and derived from C^{13} flux through a cell. K_m values were taken from the Brenda enzyme database.

The objective function to maximize urea makes this a biased system. An argument could be made that the objective function of this system of equations could be the synthesis of arginine or another anaplerotic reaction which would alter the output flux from the system. In this case, the flux of urea out of the system was maximized and reported within the Matrices.jl file.

References

[1] Park, Junyoung O et al. "Metabolite concentrations, fluxes and free energies imply efficient enzyme usage" Nature chemical biology vol. 12,7 (2016): 482-9.

[2] Jeske L., Placzek S., Schomburg I., Chang A., Schomburg D.,"BRENDA in 2019: a European ELIXIR core data resource" Nucleic Acids Res. vol. 47 (2018) BRENDA, www.brenda-enzymes.org/.