Problem Set 3

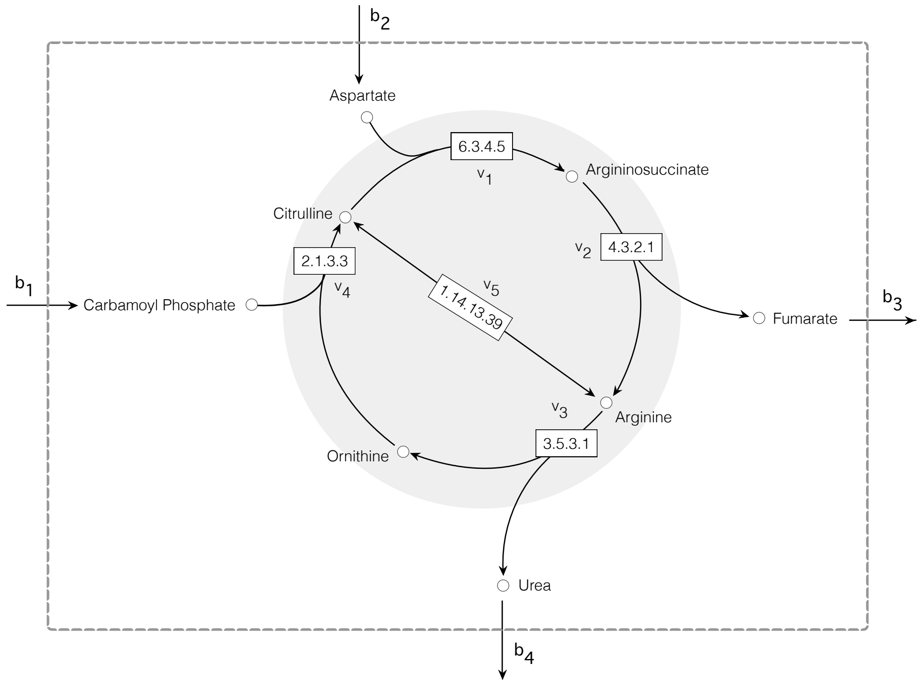

Figure 1: Schematic of the Urea cycle.

1. The urea cycle eliminates excess nitrogen from the cell (Fig. 1). Let's explore this cycle in a growing population of human cells with a doubling time of τ_d = 20 hr.

   Assume: (i) k_{cat}'s for the enzymes in the pathway are: EC:3.5.3.1 = 249s^{-1}; EC:2.1.33 = 88.1s^{-1}; EC:4.3.2.1 = 34.5s^{-1}; EC:6.3.4.5 = 203s^{-1} and EC:1.14.13.39 = 13.7s^{-1}; (ii) the approximate steady-state concentration for enzymes in the pathway (E) is uniform, and given by $E \simeq$ 0.01 μmol gDW^{-1}; (iii) use Park *et al* Nat Chem Biol 12:482-9, 2016 for K_m and metabolite concentrations to calculate the saturation term for the flux bounds (see supplemental materials); (iv) all enzymes are maximally active.

   a) Use KEGG (Arginine biosynthesis in human) to construct the stoichiometric matrix **S** for the urea cycle shown in Fig. 1.

   b) Determine if your urea cycle reconstruction is elementally balanced for C,H,N,O,P and S. If not, how can you correct the balances? (**hint**: write elemental balances around C,H,N,O,P and S).

c) Calculate the maximum rate of urea production (b_4 mmol/gDW-hr) given: 0 $\leq$b$_j$ $\leq$ 10 mmol/gDW-hr $\forall j$ using Flux Balance Analysis (FBA). If additional inputs/outputs are required, assume they obey the same bounds constraints.