

Dynamical modeling of the most important pathways in cellular metabolism

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1 Introduction

Recently, the study of cell metabolism has been in the focus of biological research, since most of the changes in cell function cause metabolic changes. Observation of these changes is usually difficult, but there are promising possibilities in metabolic pathway modeling. There is a clear need for cellular models which can predict the metabolic states and modified enzyme activity in modified states. Mitochondria which are cell organelles with prokaryotic origins have a key role in cell metabolism. Degradation of carbohydrates, fats and proteins takes place in the mitochondria, and the intermediers formed may partake in anabolic processes [1]. In our previous works we examined the intermediers of the citric acid cycle [2, 3]. These metabolites can transform to each other according to the actual metabolic state in mitochondria. The key elements in the regulation of citric acid cycle are the concentrations of intermediers and the changes in redox potential. The initial model [4] was extended by adding mitochondrial transporters which connect cellular and mitochondrial metabolic networks. The model can describe the mechanism of competitive inhibition and the function of multifunctional enzymes which play an important role in the metabolism of several different substrates.

2 Biological background

Process description

In this work we present the model complemented with several mitochondrial transporters and cellular degradation pathways. For example, glycolysis pathway contains the metabolism of glucose and fructose and leads to pyruvate. Several amino acid metabolic pathways are included, which lead to ammonia, which is then used in the urea cycle (Figure 1), and its carbon chain used by citric acid cycle or leads keton bodies (Figure 2). Using the constructed model, we analyze the temporal changes of the metabolite concentrations with a quantitative mathematical description. In this work we modeled the degradation of glucose, several amino acids and ammonia elimination via urea cycle.

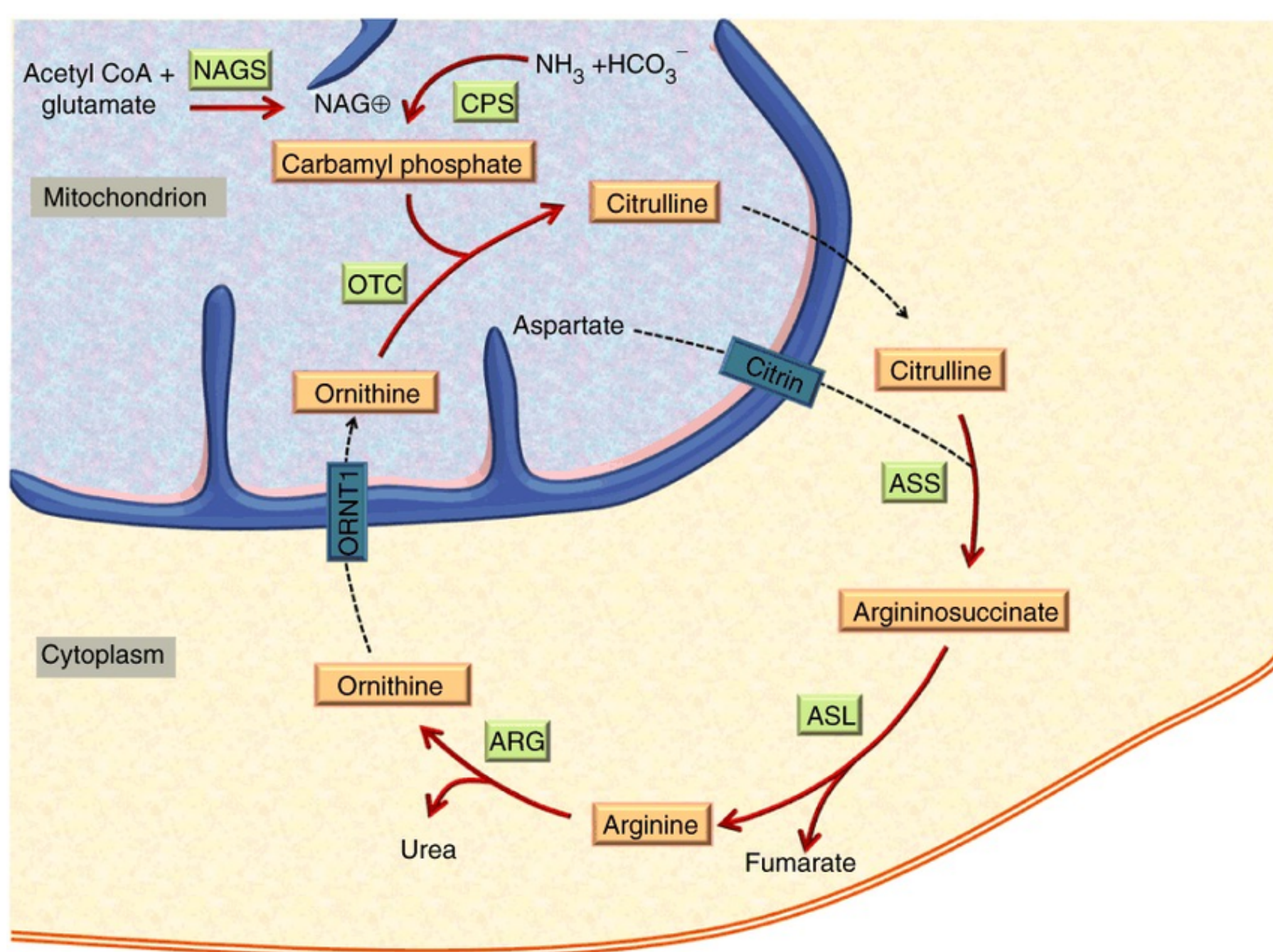


Figure 1: Urea cycle

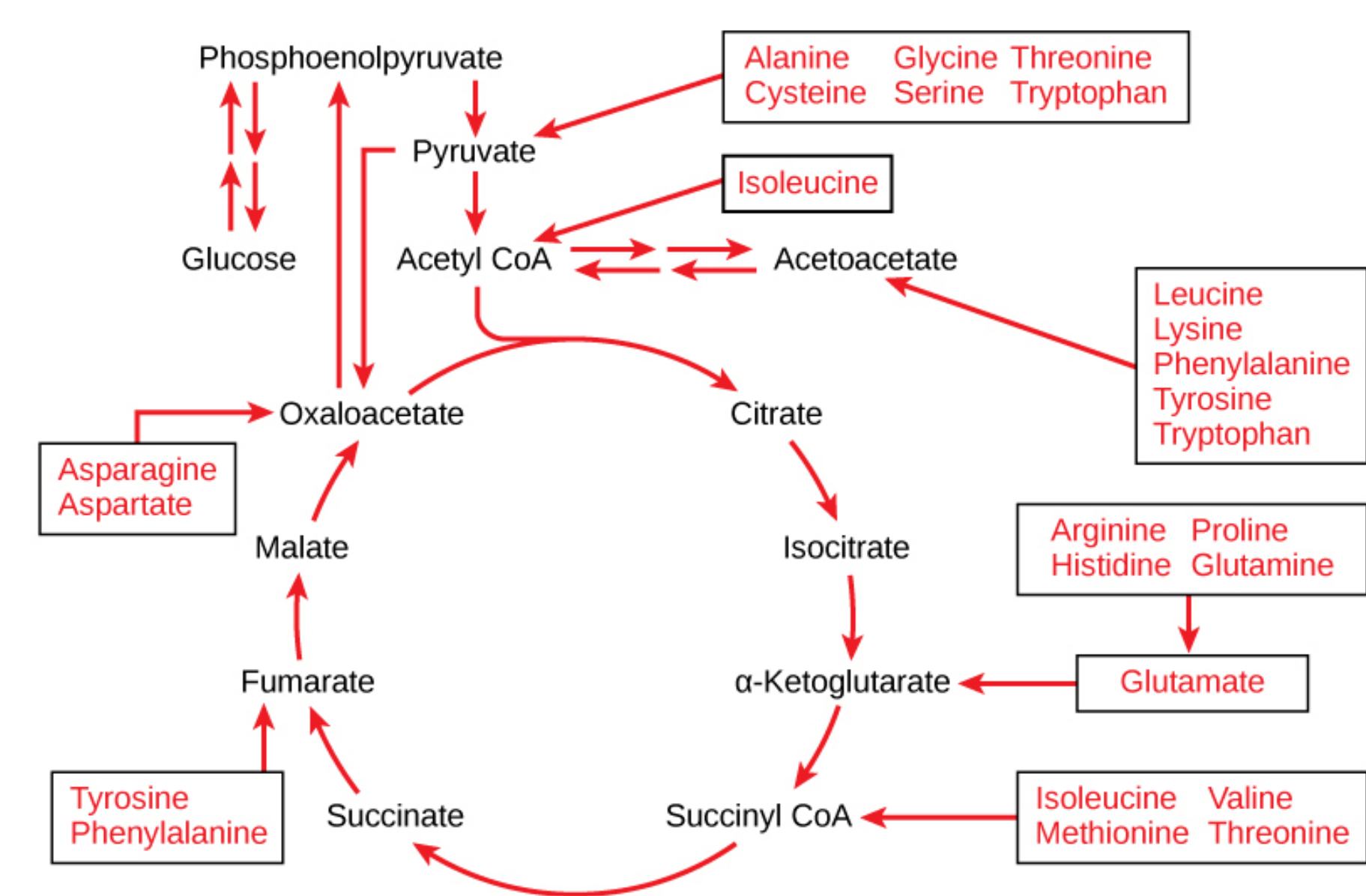


Figure 2: Amino acid metabolism

3 Kinetic model of degradation processes

3.1 Modeling goals

1. To determine the concentrations of substrates which participate in these reactions.
2. To observe the degradation methods of glucose and amino acids.

3.2 Parameters

We tested our model qualitatively (every K_m and V_{max} value are 1). This approximation is similar, which articles [5, 6] are used. Next phase in our research we would like to build exact healthy and mutant parameters to this model and test physiological and pathological metabolite conditions.

3.3 The applied kinetics

Differential equations were described by using the extended Michaelis-Menten kinetic model [5]. Rates of reversible reactions are described by two opposite reactions. The general form of the reaction rates is

$$S_1 + S_2 + \dots + S_n \rightleftharpoons P_1 + P_2 + \dots + P_k$$

$$V_{S_1, \dots, S_n} = V_{max}(E) \cdot \left(\frac{[S_1]}{[S_1] + K_m(S_1, E)} \right) \cdot \dots \cdot \left(\frac{[S_n]}{[S_n] + K_m(S_n, E)} \right)$$

$$V_{P_1, \dots, P_k} = V_{max}(E) \cdot \left(\frac{[P_1]}{[P_1] + K_m(P_1, E)} \right) \cdot \dots \cdot \left(\frac{[P_k]}{[P_k] + K_m(P_k, E)} \right)$$

$$V_{S \rightleftharpoons P} = V_{S_1, S_2, \dots, S_n} - V_{P_1, P_2, \dots, P_k} =$$

$$= V_{max}(E) \cdot \left(\left(\frac{[S_1]}{[S_1] + K_m(S_1, E)} \right) \cdot \dots \cdot \left(\frac{[S_n]}{[S_n] + K_m(S_n, E)} \right) - \right.$$

$$\left. - \left(\frac{[P_1]}{[P_1] + K_m(P_1, E)} \right) \cdot \dots \cdot \left(\frac{[P_k]}{[P_k] + K_m(P_k, E)} \right) \right)$$

Transport rates are computed with different kinetic for transporters from literature [6].

4 Computational results for simulating pathways

4.1 Model implementation

The simulations were implemented in MATLAB. We have used the ode23s solver suitable for stiff problems.

4.2 Glycolysis

In the first simulation we observe degradation of half unit glucose to one unit pyruvate, and we can see the temporal changes of intermediers (Figure 3).

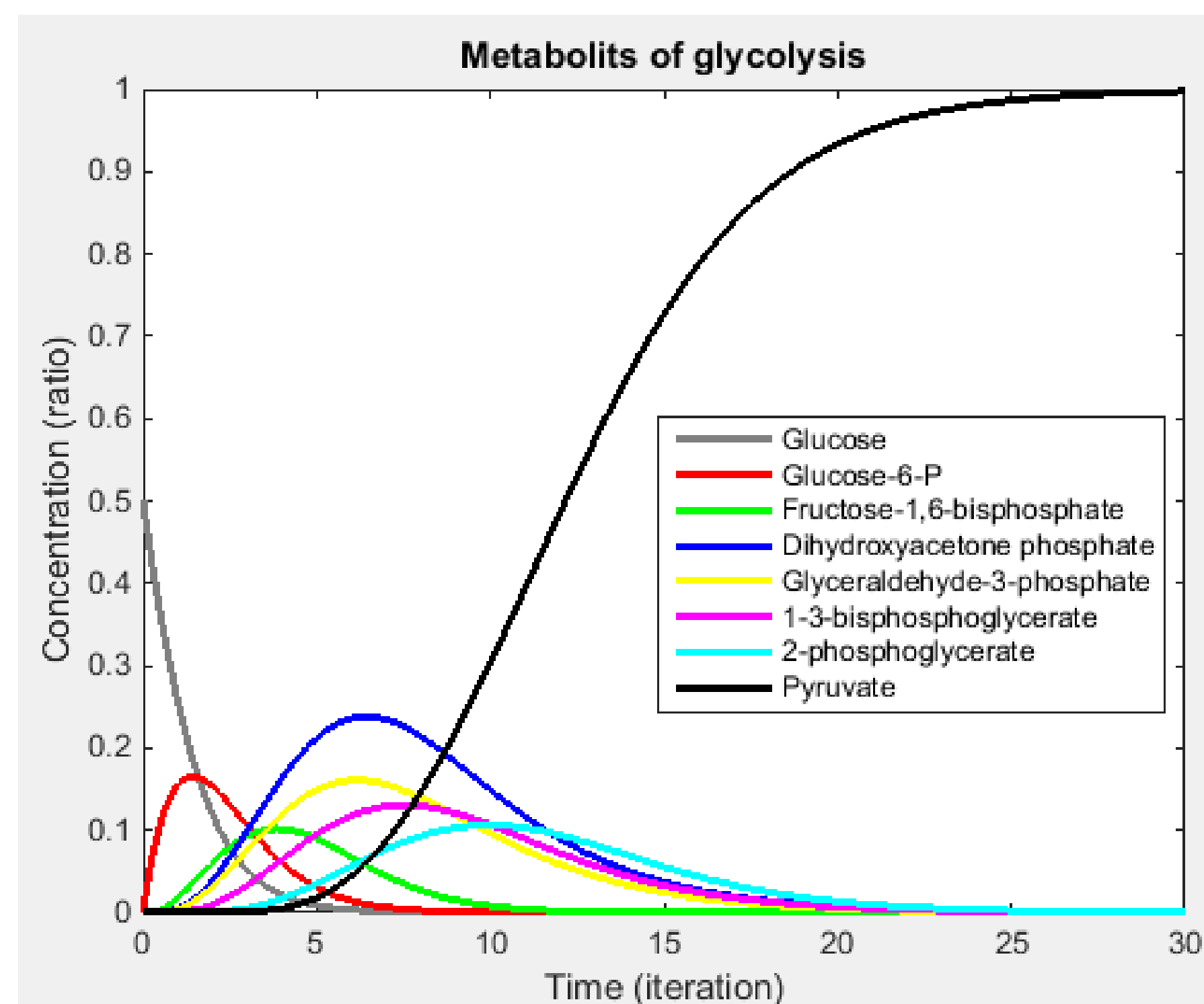


Figure 3: Metabolites of glycolysis

4.3 Urea cycle

In the second simulation we observe elimination dynamics of ammonia via urea cycle, and we can see the temporal changes of intermediers (Figure 4).

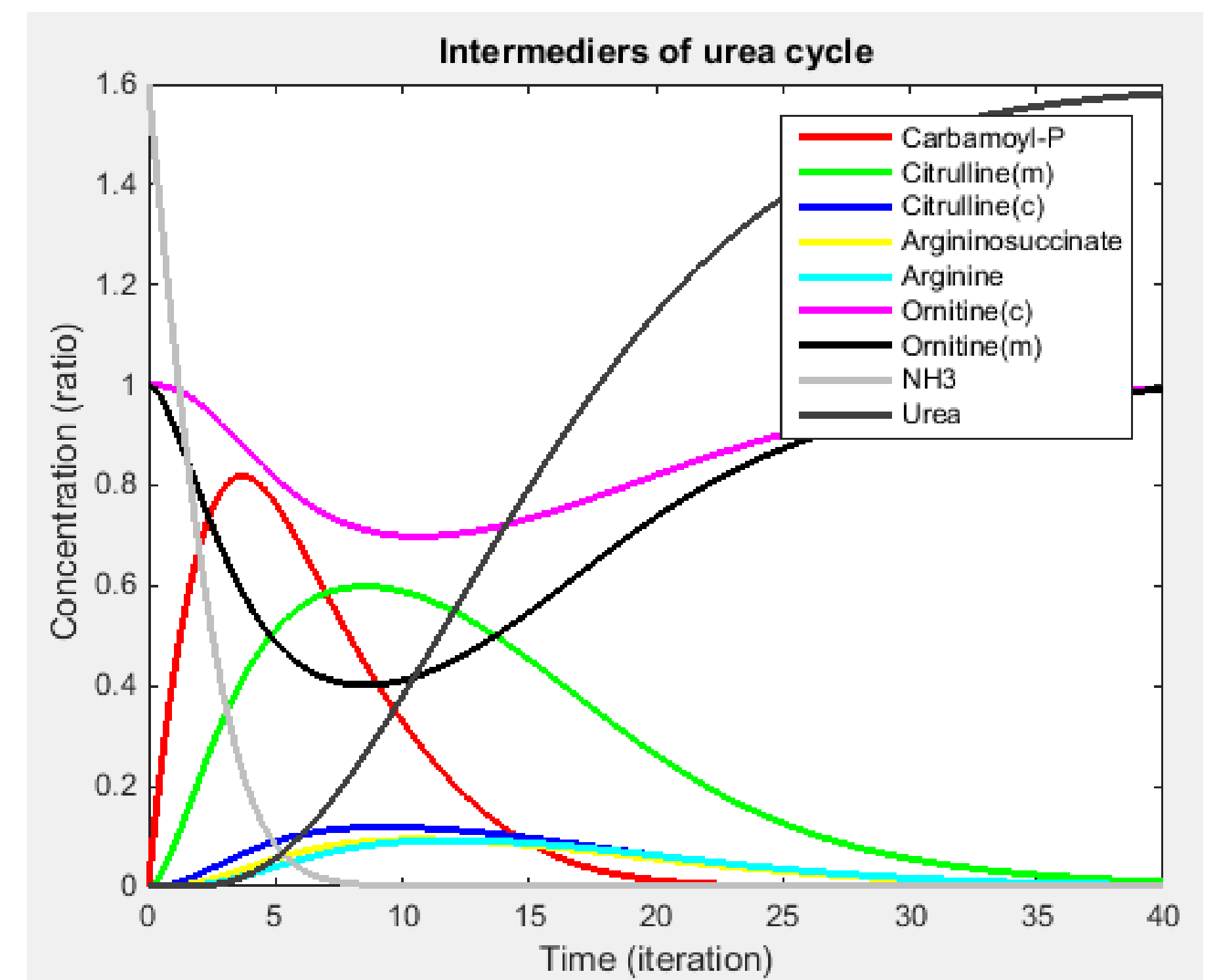


Figure 4: Intermediers of urea cycle

4.4 Gln, Glu, Asn, Asp, Ala metabolism

In the third simulation we examine the elimination dynamics of ammonia via urea cycle, and we can see the temporal changes of intermediers (Figure 5).

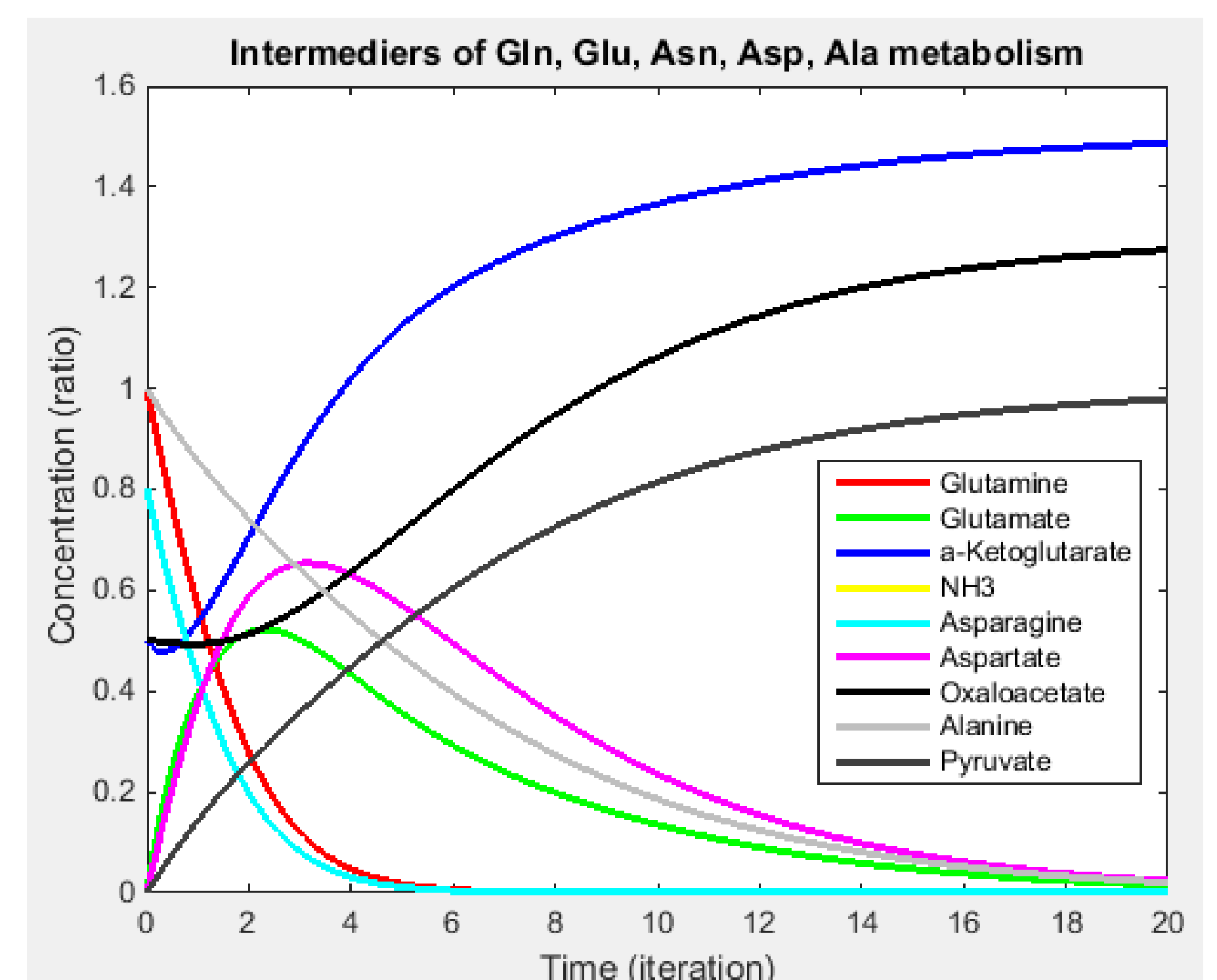


Figure 5: Intermediers of gln, glu, asn, asp, ala degradation pathways

5 Conclusion

A simple dynamic model for describing the dynamics of key quantities in glycolysis and amino acid degradation pathways was proposed in this paper. The model describes the studied processes with non-linear ODEs using Michaelis-Menten kinetics. The model was used successfully to simulate temporal changes of intermediers via these processes. Our model gives acceptable results qualitatively. If we would like to get quantitative results, we need exact parameters for each enzyme and physiological initial concentrations of metabolites and co-factors.

Acknowledgements

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