Why Is Tyrosine, More Abundant in Intracellular Proteins, Classified as a Non-Essential Amino Acid?: The Extracellular Demand Hypothesis

Esumi, Genshiro

Department of Pediatric Surgery, Hospital of the University of Occupational and Environmental Health, Kitakyushu, Japan

Abstract

In a previous report, I proposed the "Extracellular Protein Hypothesis," which posits that a consistent disparity in amino acid usage between intracellular and extracellular proteins underlies the division of amino acids into essential and non-essential classes—based on the simple concept that organisms cannot dispense with the biosynthetic pathways for amino acids used abundantly in extracellular proteins. However, in that analysis, tyrosine appears not to follow this framework: despite statistical data suggesting its higher abundance in intracellular proteins, the biosynthetic pathway for tyrosine has been retained, and tyrosine is classified as a non-essential amino acid.

Tyrosine biosynthesis is maintained via its conversion from phenylalanine, yet there is a human disorder in which this conversion ability is almost entirely lost. In such cases, the body cannot produce sufficient amounts of neurotransmitters, hormones, and pigments without dedicated tyrosine supplementation. These clinical manifestations suggest that tyrosine biosynthesis may have been preserved primarily for synthesizing these non-protein molecules with specific functions—driven by both intercellular communication needs and environmental adaptation—both of which constitute demands from the extracellular environment. Building on these insights, I propose an "Extracellular Demand Hypothesis" in addition to (or potentially replacing) the previously proposed "Extracellular Protein Hypothesis."

Keywords: Extracellular Demand Hypothesis, Extracellular Protein Hypothesis, Amino acid synthesis, Tyrosine, Evolution

Email: esumi@clnc.uoeh-u.ac.jp

1. Background

In a previous report, I proposed the “Extracellular Protein Hypothesis,” which posits that a consistent disparity in amino acid usage between intracellular and extracellular proteins underlies the division of amino acids into essential and non-essential classes—based on the simple concept that organisms cannot dispense with the biosynthetic pathways for amino acids used abundantly in extracellular proteins [1]. However, in that analysis, tyrosine appears not to follow this framework: despite statistical data indicating that tyrosine is more abundant in intracellular proteins (and thus less abundant in extracellular proteins), the biosynthetic pathway for tyrosine has nonetheless been retained, and tyrosine is classified as a non-essential amino acid [1]. To reconcile this contradiction, the earlier discussion speculated that because tyrosine is synthesized downstream of phenylalanine—an essential amino acid—the ability to synthesize tyrosine might have been lost in tandem with phenylalanine. Yet this notion still does not explain why the conversion of phenylalanine into tyrosine has been preserved, leaving tyrosine’s paradoxical, unmatched behavior unresolved.

To illustrate this discrepancy, I present here a figure and a table originating from previous works. **Figure 1** shows the eigenvectors of the first two principal components derived from the amino acid composition of all 1,954 food items in the official Japanese food composition database. (This figure is a regenerated version of what was reported in earlier papers [1,2], updated using the latest data [3], although the overall conclusion remains the same.)

In **Figure 1**, while most essential and non-essential amino acids separate clearly, tyrosine—classified as a non-essential amino acid—becomes interspersed among the essential amino acids. Previous reports hypothesized that this segregated distribution establishes the boundary between essential and non-essential amino acids and simultaneously reflects universal disparities in the intracellular versus extracellular amino acid composition of the organisms’ bodies, given that nearly all the listed food items are essentially composed of eukaryotic body parts [1, 2].

More specifically, **Table 1** (republished here) compares the intracellular and extracellular amino acid distributions in chicken meat. In this table as well, essential amino acids predominate intracellularly, whereas non-essential amino acids are more abundant extracellularly, and non-essential tyrosine again clusters with the essential group [1,4].

These findings not only suggest that the essential–non-essential boundary might indeed be grounded in the disparate amino acid compositions of intracellular and extracellular proteins, but also underscore tyrosine's uniquely anomalous status within this "Extracellular Protein Hypothesis." Seeking to understand the origin of this discrepancy—namely, why tyrosine biosynthesis has been evolutionarily retained despite tyrosine's statistical predominance in intracellular proteins (compared to that in extracellular proteins)—I turned to a clinically recognized human congenital metabolic disorder resulting from a deficiency in tyrosine biosynthetic enzyme function. Therefore, in this paper, by examining the phenotypic manifestations of this disorder, I aim to shed light on the evolutionary forces that may have conserved tyrosine biosynthesis, thereby offering a more plausible perspective on how the essential–non-essential boundary might have arisen.

2. Tyrosine Biosynthesis Defects and Related Human Disorders

2.1 Overview of Tyrosine Metabolism

Tyrosine is one of the 20 amino acids that constitute proteins and, among eukaryotic organisms capable of consuming external nutrients, it is almost uniformly classified as a non-essential amino acid [5]. Accordingly, while all 20 amino acids can be synthesized by autotrophic organisms such as plants, in animals—including humans—only the non-essential amino acids can be synthesized endogenously. Nevertheless, because all amino acids necessarily contain nitrogen—and because most amino acid molecules in animals exist as residues within proteins—the biosynthesis of non-essential amino acids in animals generally relies on the conversion of one amino acid to another.

Tyrosine is no exception. In humans and other animals, it is synthesized primarily via the hydroxylation of phenylalanine. This reaction is catalyzed by phenylalanine hydroxylase (PAH), which introduces a hydroxyl group into phenylalanine, a process that also requires the cofactor tetrahydrobiopterin (BH4) [6]. Consequently, the maintenance of normal tyrosine levels depends on two key factors: (1) the functional integrity of PAH and (2) the adequate supply and recycling of BH4. A deficiency in either—enzyme malfunction in (1) or metabolic failure in (2)—impairs tyrosine biosynthesis.

With regard to tyrosine utilization and catabolism, as with other amino acids, tyrosine can be incorporated into proteins or catabolized to enter the tricarboxylic acid (TCA) cycle for ATP production. However, tyrosine is particularly notable because it also serves as a precursor

for several critical compounds, including neurotransmitters such as catecholamines (dopamine, norepinephrine, and epinephrine) and hormones such as thyroid hormones (T3 and T4) [6]. Moreover, tyrosine is essential for the synthesis of the pigment melanin, which is responsible for coloration in hair, skin, and eyes [6].

2.2 Representative Human Disorders

As explained in the previous subsection, tyrosine biosynthesis in the human body depends on both PAH and BH4. A deficiency in the PAH enzyme or a defect in BH4 metabolism can impede tyrosine production, and such conditions are collectively termed phenylketonuria (PKU) [6]. They are grouped under PKU because disruptions in tyrosine biosynthesis are more readily identified by the accumulation of phenylalanine—tyrosine's precursor—rather than by symptoms related to decreased tyrosine levels or reduced biosynthesis. Meanwhile, the severity of PKU can vary considerably depending on the degree of enzymatic or metabolic dysfunction. Among these variants, the most severe form is "classical PKU," which is characterized by a significant loss of PAH function and, in some cases, has been reported to reduce the capacity for tyrosine synthesis to less than 1% of normal levels [7, 8]. Accordingly, this pathology most closely approximates the "loss of the capacity to convert phenylalanine into tyrosine"—in other words, the near loss of tyrosine's biosynthetic capability—that is central to this paper's investigation.

Thus, in this study, I focus specifically on the phenotype of this "classical PKU" to shed light on how such a profound impairment of tyrosine biosynthesis manifests, and to consider the evolutionary context that may have driven the retention of tyrosine's biosynthetic pathway.

2.3 Phenotypic Consequences of Classical PKU

What symptoms, then, does this classical PKU present, and which of these might stem specifically from tyrosine synthesis deficiency? When PAH function is impaired, phenylalanine first accumulates endogenously, a buildup that can be neurotoxic and lead to developmental disabilities [6]. Second—and of particular relevance here—diminished tyrosine availability reduces the synthesis of various neurotransmitters and hormones derived from tyrosine, including catecholamines (dopamine, norepinephrine, and epinephrine) and thyroid hormones (T3 and T4) [6]. Moreover, the production of melanin—the pigment responsible for the coloration of hair, skin, and eyes—also decreases [6].

Thus, among the symptoms manifested by classical PKU, those arising from impaired tyrosine biosynthesis are more likely tied to insufficient production of these non-protein functional molecules (i.e., neurotransmitters, hormones, and pigments) rather than to a general shortfall in amino acids for protein synthesis. Deficits in neurotransmitter and hormone production disrupt endocrine-mediated bodily control, while impaired pigment synthesis leads to reduced pigmentation or a whitening of the body's coloration—akin to the albinism phenotype that increases vulnerability to ultraviolet radiation. Although albinism is generally attributed to enzymatic defects in the tyrosine-to-melanin pathway, patients with conditions such as classical PKU who do not receive dedicated tyrosine supplementation may display similar symptoms [6].

This section thus provides an overview of the metabolic conversion from phenylalanine to tyrosine, the disorder known as phenylketonuria (resulting from a defect in this pathway), and the phenotypes and symptoms that emerge when tyrosine biosynthesis is severely compromised.

3. Discussion

3.1 The Role of a Congenital Enzyme Deficiency in Explaining Tyrosine's Anomalous Behavior

The purpose of this paper is to determine whether the anomalous behavior of tyrosine—described under the previously proposed "Extracellular Protein Hypothesis" [1]—could be explained by the pathophysiology and phenotype of a congenital deficiency in the relevant enzyme. In experimental biology, the necessity of a particular metabolic pathway is typically investigated by examining the phenotype of knockout models in which that pathway is disabled. Although this paper does not involve generating such knockout animals, I hypothesized that the human metabolic disorder known as classical PKU, along with its underlying pathology and clinical presentation, could serve a comparable explanatory function. I therefore investigate whether the symptoms of classical PKU account for the conserved capacity to convert phenylalanine into tyrosine.

Generally speaking, one might assume that the greatest demand for intracellular amino acids lies in protein synthesis. However, my findings suggest that losing tyrosine's biosynthetic capacity does not result in a shortage of amino acids for protein synthesis; instead, it leads to deficits in functional molecules such as neurotransmitters, hormones, and pigments. This

outcome implies that evolutionary pressure to maintain tyrosine biosynthesis was likely driven by the necessity of these functional molecules, rather than by a need for raw materials in protein assembly.

3.2 Could Tyrosine's Biosynthetic Capacity Be Lost?

Is it even possible for organisms to lose the capacity to synthesize tyrosine? And what about other species? As far as the literature indicates, across all three domains of life, only a very small number of species appear to have lost the ability to synthesize tyrosine [5].

Let us consider the loss of amino acid biosynthetic capacities. It is generally believed that the earliest life forms on the evolutionary tree possessed the capacity to synthesize all amino acids. At some point along the lineage leading to modern humans, the biosynthetic pathways for what are now considered "essential amino acids" were lost. To understand how this occurred, recall that genetic mutations arise more or less randomly in all individuals and all lineages, and only the non-lethal mutations are passed on, since organisms with lethal mutations fail to leave offspring. Under this reasoning, the loss of biosynthetic capacity for so-called "essential amino acids" must have been non-lethal, whereas the loss of capacity for "non-essential amino acids" would have been lethal.

According to the previously mentioned "Extracellular Protein Hypothesis," losing the capacity to synthesize amino acids predominantly used in extracellular proteins would be lethal, thereby defining the boundary between essential and non-essential amino acids. By that logic, if tyrosine were more abundant in intracellular proteins, losing its biosynthetic capacity would presumably not be lethal.

Yet in reality, tyrosine's biosynthetic capacity has not been lost, and tyrosine is classified as a non-essential amino acid. Considering that most organisms across the three domains retain the ability to synthesize tyrosine, one may inductively infer that losing tyrosine biosynthesis is lethal in almost all cases. In this study, I focus on classical PKU in humans, hypothesizing that its clinical symptoms offer insights into the lethal background underlying tyrosine's retention. Indeed, no reports of complete PAH inactivity have been identified even in classical PKU, implying that a total loss of tyrosine biosynthesis might be lethal for other reasons [6]. However, because this paper cannot examine such scenarios in greater detail—a limitation of this study—I will proceed by analyzing the symptoms of classical PKU to derive further insights.

3.3 Which Factor Drives the Retention of Tyrosine Biosynthetic Capacity?

Among the tyrosine-deficiency symptoms manifested in classical PKU—namely, depletion of neurotransmitters, hormones, and pigments—which would have been the most lethal over the course of evolutionary history?

First, consider neurotransmitters and hormones. These signaling molecules have long enabled multicellular organisms to coordinate cellular activities and function in unison. However, from an evolutionary standpoint, it is plausible that the tyrosine-derived signaling molecules we see today emerged only partway through the evolution of multicellularity. For instance, in relatively primitive organisms like *Hydra*, only peptide-based signaling molecules have so far been identified, intercellular signaling is hypothesized to rely solely on peptides rather than amino-acid-derived molecules such as catecholamines [9]. Thus, it is unlikely that early multicellular life depended on tyrosine-derived intercellular signaling molecules, raising doubts that losing tyrosine biosynthesis would be lethal solely to preserve these compounds.

What, then, about pigment synthesis? Pigment biosynthesis is observed not only in eukaryotes but also in certain prokaryotes, including bacteria capable of producing melanin [10]. One hypothesis posits that, as life transitioned from marine to terrestrial environments, organisms faced significant DNA damage due to increased ultraviolet radiation. Pigment production—especially melanin—is believed to have evolved partly as a defense against UV damage. Given the vast diversity of life, the widespread presence of coloration in many species—and the relative rarity of fully unpigmented (albino) organisms—suggests that pigment production is nearly universal for survival, presumably in open, natural habitats. By this reasoning, losing tyrosine biosynthesis would hamper pigment production, thereby imposing a constraint that helps preserve tyrosine synthesis. Based on the current analysis, this possibility appears most compelling.

3.4 Existing Hypothesis: The Extracellular Protein Hypothesis

At this point, it is worth revisiting the “Extracellular Protein Hypothesis” I previously proposed. This hypothesis holds that the disparity in amino acid composition between intracellular and extracellular proteins—the so-called “amino acid distribution gap”—defines the boundary between essential and non-essential amino acids. The underlying premise is that, unlike intracellular resources, extracellular proteins are more difficult to recycle once they leave the cell. Consequently, there would have been an economic selective pressure favoring low-synthesis-cost amino acids in extracellular proteins. This, in turn,

created a bias in amino acid composition. Furthermore, to sustain the synthesis of extracellular proteins containing certain amino acids, organisms had to retain the biosynthetic (or interconversion) pathways for those amino acids. I hypothesized that the essential–non-essential boundary might not be incidental, but rather an inevitable outcome of evolutionary pressures.

3.5 Reconciling Tyrosine's Exception: The Extracellular Demand Hypothesis

Herein lies the dilemma posed by tyrosine's anomalous behavior. According to the Extracellular Protein Hypothesis—i.e., that amino acids more abundant in extracellular proteins must retain their biosynthetic pathways—tyrosine, which is more abundant in intracellular proteins, should not have required such capacity. Yet this is contradicted by evidence that tyrosine biosynthesis has been retained. Focusing on the clinical disorder classical PKU in humans, I conclude from its symptoms that losing tyrosine biosynthesis leads to deficiencies in functional molecules such as intercellular signaling compounds and pigments. In particular, I hypothesize that losing pigment synthesis played a critical role in the evolutionary retention of tyrosine biosynthesis.

Both intercellular signaling and pigment production can be viewed as demands originating from the extracellular environment—one for coordinating external interactions between cells, and the other for adapting to hazards such as UV radiation. Accordingly, I propose an "Extracellular Demand Hypothesis," suggesting that tyrosine's retained biosynthetic capacity is best explained by these external pressures.

Although I refer to this new theory as the "Extracellular Demand Hypothesis," the original "Extracellular Protein Hypothesis" also hinges on demands from the extracellular environment—namely, the necessity of building extracellular structures from low-synthesis-cost amino acids. From this perspective, one might combine the older hypothesis under a broader framework of extracellular demands. However, to maintain clarity, I have chosen to keep these two ideas distinct: the "Extracellular Protein Hypothesis" sets the overall essential–non-essential boundary, while the "Extracellular Demand Hypothesis" accounts for tyrosine's exceptional behavior within that boundary.

3.6 On the Evolutionary Origins of Essential and Non-Essential Amino Acids

Why did humans cease synthesizing certain amino acids, and what eventually defined the boundary between essential and non-essential amino acids? These evolutionary questions—akin to asking why humans have five fingers—are virtually impossible to verify through

direct experimentation. Consequently, any explanations must rely on inductive reasoning and will inevitably remain incomplete. In the present study, by examining a disorder that fortuitously aligns with the phenotype of interest, I have proposed a hypothesis that offers at least a partial answer to these fundamental queries. While imperfect inductive approaches may be our only option at this stage, future advances in computational methods may permit simulations that can tackle these evolutionary puzzles more rigorously. We can look forward to technological developments that could make such analyses increasingly feasible.

4. Conclusion

In this paper, I investigated the anomalous behavior of tyrosine within the context of classical PKU—a condition characterized by a congenital deficiency in the enzyme responsible for tyrosine biosynthesis—while revisiting the previously proposed "Extracellular Protein Hypothesis," which explains the boundary between essential and non-essential amino acids by considering the demands of extracellular protein synthesis. The findings in this study indicate that tyrosine plays a critical role as a precursor for functional molecules such as intercellular signaling compounds and pigments. Therefore, I inferred that tyrosine's biosynthetic pathway has been exceptionally retained to ensure the continued production of these functional molecules. Consequently, I term this explanation the "Extracellular Demand Hypothesis," and together with the previously proposed "Extracellular Protein Hypothesis," I propose it as a new framework for understanding the origin of the essential–non-essential boundary.

5. Reference

1. **Esumi, G.** (2024). Why we stop synthesizing essential amino acids: The Extracellular Protein Hypothesis [Preprint]. Jxiv. https://doi.org/10.51094/jxiv.618

2. **Esumi, G.** (2020). Autophagy: possible origin of essential amino acids [Preprint]. *Cambridge Open Engage*. https://doi.org/10.33774/coe-2020-lll03

3. **Ministry of Education, Culture, Sports, Science and Technology [MEXT].** (2020). 日本食品標準成分表2020版（八訂） アミノ酸成分表編 第2章第1表 [Standard tables of food composition in Japan 2020 (Eighth revised edition), amino acid composition table, Chapter 2, Table 1]. Retrieved January 15, 2025, from https://www.mext.go.jp/a_menu/syokuhinseibun/index.htm

4. **Karatzas, C. N., & Zarkadas, C. G.** (1989). Comparison of the Amino Acid Composition of the Intracellular and Extracellular Matrix Protein Fractions Isolated from Avian Skeletal Muscles. *Poultry Science, 68*(6), 811–824. https://doi.org/10.3382/ps.0680811

5. **Gietzen, D. W., & Rogers, Q. R.** (2006). Nutritional homeostasis and indispensable amino acid sensing: a new solution to an old puzzle. *Trends in Neurosciences, 29*(2), 91–99. https://doi.org/10.1016/j.tins.2005.12.007

6. **Donlo, J., Sarkissian, C., Levy, H., Scriver, C. R.** (2019). Hyperphenylalaninemia: phenylalanine hydroxylase deficiency. Valle D.L., & Antonarakis S, & Ballabio A, & Beaudet A.L., & Mitchell G.A.(Eds.), The Online Metabolic and Molecular Bases of Inherited Disease. McGraw-Hill Education. https://ommbid.mhmedical.com/content.aspx?bookid=2709&sectionid=225081923

7. **Woo, S. L. C., Lidsky, A. S., Güttler, F., Chandra, T., & Robson, K. J. H.** (1983). Cloned human phenylalanine hydroxylase gene allows prenatal diagnosis and carrier detection of classical phenylketonuria. *Nature, 306*(5939), 151–155. https://doi.org/10.1038/306151a0

8. **Friedman, P. A., Fisher, D. B., Kang, E. S., & Kaufman, S.** (1973). Detection of Hepatic Phenylalanine 4-Hydroxylase in Classical Phenylketonuria. *Proceedings of the National Academy of Sciences, 70*(2), 552–556. https://doi.org/10.1073/pnas.70.2.552

9. **KOIZUMI, O. (1999).** The neurobiology of the diffuse nervous system of the hydra. *Hikaku Seiri Seikagaku(Comparative Physiology and Biochemistry), 16*(4), 278–287. https://doi.org/10.3330/hikakuseiriseika.16.278

10. **Césarini, J. P.** (1996). Melanins and their possible roles through biological evolution. *Advances in Space Research, 18*(12), 35–40. https://doi.org/10.1016/0273-1177(96)00025-7

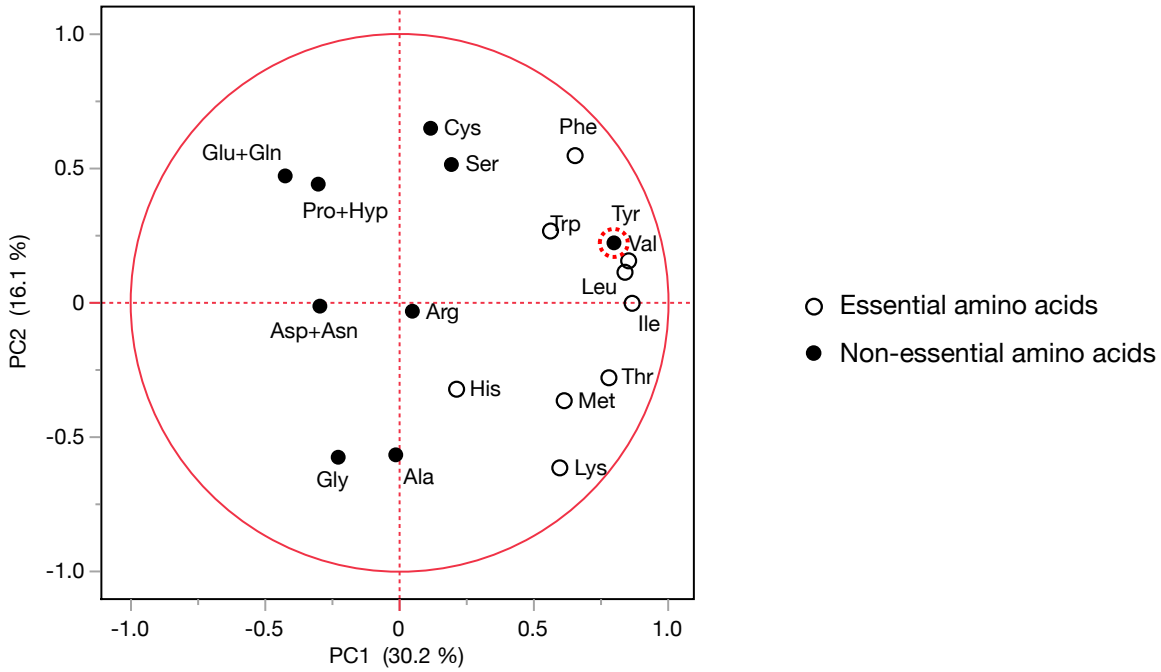

Figure 1. Eigenvector Plot of Food Amino Acid Composition (Principal Component Analysis)

Eigenvector plot of the first two principal components (PC1 and PC2) derived from the amino acid composition of all 1,954 food items in the latest official Japanese food composition database [3], following the methodology described in previous reports [1,2]. Open circles represent essential amino acids, while filled circles represent non-essential amino acids. Although tyrosine (Tyr), highlighted by the red dotted circle, is classified as non-essential, it clusters among the essential amino acids. The percentages next to each axis label indicate the proportion of variance explained by the respective principal component.

	Intracellular compositions				Extracellular compositions				LN(Extra/Intra)					
Amino Acids	6mo Leg	1.2yr Leg	6mo Breast	1.2yr Breast	6mo Leg	1.2yr Leg	6mo Breast	1.2yr Breast	6mo Leg	1.2yr Leg	6mo Breast	1.2yr Breast	Averages(↓)	Essentiality
Pro+Hyp	0.0429	0.0410	0.0425	0.0413	0.2064	0.2117	0.2077	0.2006	1.572	1.642	1.587	1.581	1.595	●
Gly	0.0559	0.0561	0.0572	0.0547	0.2638	0.2851	0.2702	0.2689	1.552	1.626	1.553	1.592	1.580	●
Ala	0.0763	0.0785	0.0771	0.0776	0.0967	0.1011	0.0979	0.0940	0.237	0.253	0.240	0.192	0.231	●
Arg	0.0537	0.0544	0.0545	0.0535	0.0556	0.0554	0.0522	0.0505	0.034	0.018	0.043	0.058	0.012	●
Ser	0.0491	0.0500	0.0492	0.0499	0.0354	0.0331	0.0375	0.0403	0.327	0.413	0.271	0.214	0.306	●
Glu+Gln	0.1422	0.1384	0.1401	0.1404	0.0912	0.0891	0.0904	0.0961	0.444	0.440	0.438	0.379	0.425	●
Asp+Asn	0.0964	0.0982	0.0985	0.0970	0.0582	0.0553	0.0562	0.0603	0.503	0.573	0.560	0.475	0.528	●
Cys	0.0112	0.0067	0.0069	0.0111	0.0061	0.0033	0.0069	0.0043	0.612	0.728	0.011	0.936	0.566	●
Thr	0.0521	0.0517	0.0515	0.0522	0.0242	0.0211	0.0244	0.0271	0.767	0.894	0.746	0.657	0.766	●
Phe	0.0344	0.0330	0.0339	0.0336	0.0163	0.0154	0.0165	0.0145	0.745	0.763	0.720	0.837	0.767	●
Lys	0.0872	0.0874	0.0872	0.0873	0.0382	0.0390	0.0353	0.0391	0.825	0.807	0.903	0.803	0.835	●
Val	0.0629	0.0675	0.0659	0.0644	0.0285	0.0232	0.0299	0.0265	0.792	1.067	0.789	0.889	0.884	●
Leu	0.0899	0.0898	0.0896	0.0900	0.0349	0.0308	0.0349	0.0346	0.946	1.068	0.943	0.956	0.978	●
Ile	0.0555	0.0563	0.0557	0.0560	0.0190	0.0153	0.0185	0.0183	1.070	1.301	1.101	1.116	1.147	●
Met	0.0266	0.0270	0.0263	0.0273	0.0083	0.0073	0.0065	0.0086	1.163	1.313	1.405	1.156	1.259	●
Tyr	0.0300	0.0291	0.0302	0.0288	0.0093	0.0071	0.0077	0.0085	1.172	1.406	1.365	1.220	1.291	●
His	0.0256	0.0277	0.0267	0.0266	0.0078	0.0065	0.0071	0.0077	1.187	1.446	1.324	1.235	1.298	●
Trp	0.0081	0.0074	0.0071	0.0084	-	-	-	-	-	-	-	-	-	●

Table 1. Intracellular vs. Extracellular Amino Acid Composition in Chicken Skeletal Muscle

This table presents the molar compositions of amino acids in the intracellular and extracellular compartments of chicken leg and breast skeletal muscle tissue, measured at 6 months and 1.2 years of age. It was originally created and published in Reference [1], from which it is reproduced here. The raw measured values were first reported in Reference [4]. In this table, those values were converted from mass to molar quantities, and each compartment was normalized so that its total amino acid content equals one. The columns labeled "LN(Extra/Intra)" provide the natural logarithm of the ratio of extracellular to intracellular abundance, highlighting differences in distribution between the two compartments. Amino acids are arranged according to their average logarithmic ratios across all four tissue sample types. To make the data more visually accessible, each logarithmic value is overlaid with a color bar—somewhat arbitrarily scaled but aligned with the boundary between essential and non-essential amino acids. The rightmost column indicates each amino acid's essentiality in humans, where blue circles on the right denote non-essential amino acids and red circles on the left denote essential amino acids. Although the data show a general tendency for non-essential amino acids to be more abundant extracellularly, while essential amino acids predominate intracellularly, tyrosine—indicated by a small arrow from the lower-right—is an exception: it appears among the other essential amino acids despite being classified as non-essential.