Release Notes 2021-12-22 : : This is an extract from a longer (thesis length) work(explaining results feeding amino acids etc to older dogs) that is taking forever to organize and I wanted to get something out today. It motivates complexities with interpreting amino acid levels as a basis for picking an intervention but is discussed as a more general problem perceiving paradigms as paradoxes. The equation probably appears somewhere in other literature, I found a quote from the kidney lit expressing the sentiment, but I did not bother to look. It could certainly use some cleanup but seems to make the immediate points. Several peripheral points are not well documented. This is bad scholarship but can be fixed if they become important. To say the least, the paradox/paradigm point is very simplistic and intended for a variety of audiences but not sure if it is well suited for any one in particular.
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The Paradox Paradigm: When Could Amino Acid Supplements Be Beneficial?

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Amino acids are important components of proteins but also consumed as signalling molecules such as neurotransmitters or oxidized as fuel. They may also be modified non-enzymatically creating amino acid analogs that may act as the parent molecule to some degree. Blood concentrations of specific amino acids or proteins may be obvious clues about possible benefits of supplementation but that need not be the case. This paradox is elaborated by examining various correlations and contrasting them to interventions but then rationalizing with simple general equations and feedback mechanisms. While details are lacking and the model is greatly simplified, overall conservation laws, things like global nitrogen balance, are considered as sanity checks on the concentration-sufficiency assumption. Illustrations with the hypertension literature and recent amino acid profiles in covid-19 patients are considered along with some support from the dementia and kidney disease literature. Regulation patterns may be altruistic, shuttling scare amino acids from muscles to the brain, as has been observed with biotin for example. In this case, blood levels may be fortuitously normal but the 'direction" of flow is an unsustainable compensation perhaps for low glucose due to some other reason. Assays often include "damaged" components in the case of proteins and these may be elevated due to conservation measures but supply may still benefit from supplements. In brief, the paradox is due to mistaking a concentration for a velocity or flux.

1. INTRODUCTION

There is a lot of literature on blood concentrations of amino acids and proteins in health and disease. There is also literature on overall nitrogen balance attempting to add up input and outputs and determine if it is being accumulated or depleted. However, it is not clear how correlations between blood levels relate to disease modifying interventions or cures. Some of the discrepancies between correlations and "obvious" interventions are discussed after the introduction of a general rate equation as a focus for discussion. Hopefully this can point to more useful interventions or at least more informative failures.

2. ANALYSIS

Most molecules in the blood such as amino acids can be described as coming from some source "a" and going to some destination "b" while the latter may include modification without exit from the blood stream. Consider a general rate equation as follows,

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$$\frac{d[x_i]}{dt} = \sum_j a_{i,j} - [x_i] \sum_k b_{i,k} \tag{1}$$

where $[x_i]$ is the concentration of some molecule such as an amino acid, $a_{i,j}$ is a production rate from source j for x_i and $b_{i,k}$ is a consumption rate constant for some sink k. In the present cases, sources can include the GI tract or muscle and sinks can be organs such as muscle and brain, or the urine. These include components from metabolic transformations such as conversions from one amino acid to another or conversion into neurotransmitters. The source and sink values may be adaptive and vary with other parameters. Usually the thing that matters most is the consumption rate(s) , $[x_i]b_{i,k}$, which can be optimized independently via "b" but total consumption and $[x_i]$ is limited by production rate.

In steady state the blood level or concentration is,

$$[x_i] = \frac{\sum_j a_{i,j}}{\sum_k b_{i,k}} \tag{2}$$

which may be important if this level modifies the properties of the blood or the consumers are not adaptive. Otherwise, the consumption rates matter and these may be compromised in times of nutrient shortages or stress requiring "repair" while maintaining some normal concentrations. The time constant related to the circulation time for molecules of x_i is

$$\tau_i = \frac{1}{\sum_k b_{i,k}} \tag{3}$$

and

$$[x_i] = \tau_i \sum_j a_{i,j} \tag{4}$$

suggesting that the same blood level can be obtained with varying production rates and lifetimes (production and consumption velocity vectors or "directions" could be defined as $\overrightarrow{\mathbf{a_i}}$ and $[x_i]\overrightarrow{\mathbf{b_i}}$).

As τ increases, , more may be destined for spontaneous modification and may still function somewhat as the parent molecule especially with proteins.

In the case of multiple deficiencies, amino acid consumption may increase as a compensatory measure raising blood levels but not indicating excess. Effects such as this lead to changes in blood levels that do not relate to sufficiency in obvious ways. In this case, the expectation that deficiency leads to low blood levels, an assumed correlation, may discourage useful interventions rather than encourage useless ones as is often the case. Ideally, the other deficiencies would be fixed but if amio acids have been mobilized for any length of time replacing them is still likely to be beneficial. The discrepancy between correlations and interventions is explored in some limited literature from hypertension, dementia, kidney disease, and covid-19 .

2.1. Hypertension

Hypertension literature is an excellent example of this issue. While not exhaustive by any means, this selection appears reasonably representative. Studies of correlations are interpreted to suggest amino acids are not a factor. A 2019 review works on amino acids and hypertension was inconclusive [22] but the literature reviewed mostly explored plasma amino acids and blood pressure. High levels of blood BCAA's were found to be predictive of developing hypertension [7] . BCAA's sound even more suspicious as correlations between known risk factors and blood levels of BCAA's have been observed [8] . Protein or amino acid intake studies however have shown a protective effect of higher consumption of some amino acids inferred from diet [12] or mixed results [32] or in favor of trendy plant based diets [31]. A BCAA intake study suggested higher consumption was beneficial [11] and even beneficial in cirrhosis patients with portal hypertension [16] . Lysine supplementation was shown to improve hypertension in a small group of adults in Ghana [33]. Tryptophan normalized high blood pressure within 2 hours in a group of 14 patients [4]. Showing a consistent benefit from just tryptophan may require good patient selection or a combination of nutrients but none of them need demonstrate low blood concentrations. Tyrosine administration to spontaneously hypertensive rat reduced blood pressure but the effect was blocked by other large neutral amino acids [29] and one small trial on mildly hypertensive people failed to show a benefit [27].

The apparent inconsistency between correlation and intake trials can be resolved with hypothesized causality and the source and sink equations above. For example, muscle uptake can be reduced in starvation even at a fixed plasma level [34] which may allow for more amino acids to be used for gluconeogenesis. (Interestingly, in older people there is some indication muscles increase amino acid export after exercise [3] which would be an altruistic move anticipating brain requirements. As precedent, biotin altruism among SMVT expressors has been observed.) In this case, intervention trials would make sense even lacking associations between low plasma levels and BP.

2.2. Dementia

Dementia appears to be another area where amino acid profiles don't follow glib expectations. One case of amino acid profiling in elderly dementia patients demonstrates increases in serine, arginine, and isoleucine [26] Similarly, increased amino acids in CSF for dementia patients (methionine and alanine) [19] have been observed. In cases where the brain's glucose metabolism is impaired, amino acid oxidation may make up the difference [10] further contributing to loss and probably mobilization from various reserves increasing concentrations in fluids. Interestingly, as a possible confounding or alternative effect, insulin and glucose were shown to increase Trp and Tyr in the brain while decreasing serum levels suggestive of transport into the CNS [30] although the situation is complicated by factors including competing amino acids binding to albumin [2] . While serum tryptophan was shown to correlate with cognitive impairment in a small group of older women [23] , it was elevated in cancer patients [14] who probably do not have excess protein supply. If this is compensatory or maladaptive is unknown.

Limited intervention trials however have shown promise. As early as the 1970's, brain neurotransmitters including acetylcholine , were found to be responsive to dietary precursor inputs to varying degrees [5]. Neurodegeneration was corrected in one mouse model with essential amino acids and the authors point out there is epidemiological association with senile dementia [24] suggesting the result is applicable to real disease. . An intervention trial with "Amino LP7" on adults 55 and older with other criteria demonstrated benefits in various aspects of functioning [28] but that likely can be improved due to considerations discussed here and in forthcoming work.

Lithium was recently found to suppress tryptophan catabolism [9] although a role for tryptophan depletion in mental disorders did not appear to be considered. Many drugs such as MAO inhibitors ultimately conserve products derived from amino acids and therefore could conserve the amino acids. SSRI's, MAOI's, anti-histamines, etc could all be expected to change fluxes and adjust control mechanisms.

2.3. Kidney Disease

Kidney disease is often considered in terms of modification to protein intake but recommendations vary. In this context, serum albumin illustrates problems with protein assays. Serum albumin as with all proteins has many modified forms both physiological and pathological [15] [25] [21] [1] so trying to measure a "total" amount may be uninformative for nutritional interventions. Longer circulation lifetime which may occur with conservation attempts likely allow for more damage as is thought to occur with fibrinogen [18]. The multiple effects on source and sink have been noted for kidney patients [6] ,

> Despite its sensitivity as a screening and prognostic tool, serum albumin provides limited information about the complex nature of the underlying nutritional problem in the setting of AKI and CKD. The albumin concentration is the net result of its synthesis, breakdown, the volume of distribution, and exchange between intra- and extra-vascular spaces, as well as losses [75]. Besides, it is a negative acute phase reactant, i.e., during acute illness its synthesis is reduced, resulting in low serum levels. Albumin level values should not be interpreted alone, and the appropriate nutritional assessment should also include a thorough physical exam and clinical judgment [76].

While high protein diets with kidney disease are controversial, some consideration of "protein quality" exists [13] and its even possible that specific amino acid deficiencies contribute to kidney disease . In the specific case of kidney, protein and in particular tyrosine are important issues although glutamine supplementation is thought to be harmful [6] which itself has been a surprising or "paradoxical" result even as I had not recommended that [17] but suggested it could be synthesized from the TCA and "waste" nitrogen sources.

It has been said [20] ,

> A deficiency of even a single AA leads to a negative nitrogen balance. In this state, more protein is degraded than is synthesized, so more nitrogen is excreted than is ingested (38). The latter is particularly relevant for CKD patients under low protein diet (LPD), who may be at risk for developing protein-energy wasting (PEW) if not adequately monitored.

In theory large proteins could be catabolized to gain a few necessary amino acids leaving the rest as waste products. In such a case, essential amino acids even in slight surplus, would be beneficial over wasting large amounts of nitrogen. Urinary protein "wasting' could reflect the only means to eliminate crosslinked/modified proteins or simply eliminating excess scavenged proteins(the "haystack" as the "needle' is found).

2.4. covid-19

Various derangements were observed in covid-19 patients [17] but with no clear interpretation. Given the descriptions of hypermetabolism, GI infections, and immune activation, its most reasonable to assume essential amino acids were depleted and elevated blood levels are clues about some compensatory actions not surplus. Interestingly, the much discussed ACE2 is associated with amino acid transport which is largely ignored. My work is explicitly concerned with tyrosine isomers which have significant existing literature but have not been studied in covid-19 or in relation to coagulation status.

2.5. Discussion

These paradoxes, successful interventions that don't seem consistent with blood levels , may ba a pattern or actually a paradigm covered by the general rate equation although other issues may cloud correlation studies. Headlines about vitamin D associations with various health outcomes are much more numerous than successful intervention trials. In this case, vitamin D status could correlate with fat soluble nutrient absorption and suggest issues with vitamin K or lipophilic amino acids. With neutrophils, the left shift is known to indicate velocity but those clues may not exist for other quantities. A1c is an integrated damage measure but that may also depend on RBC half life (another dynamical component usually negligible). With amino acids, there is a lot of unexplored territory but once the correlation studies are considered less discouraging when a hypothesis on cause and effect exists, interventions such as those I proposed earlier make a lot more sense. In the case of older people with impaired digestion and intake or protein wasting in the urine, amino acid supplements may make sense especially with any empirical indications of benefit absent randomized controlled clinical trials.

With blood sugar, high blood sugar causes damage as measured with "A1c" but also often represents a failure to consume the sugar. Some damage may be avoided by reducing supply or wasting it, but ultimately there is likely a problem with consuming it that should be fixed.

In reality, many patients have issues with diet or GI tract making protein deficiency a reasonable suspect. In other cases, with protein wasting via the kidneys, even more amino acids may be needed even if protein wasting is thought to be related to excess protein. Tryptophan in particular may be a concern due to its scarcity, physical properties, and immune activated destruction.

While it remains to be determined if results hold up in definitive well controlled clinical trials, limited Intervention trials can be successful contrary to what may be expected based on correlation studies.

3. CONCLUSIONS

In many cases, where negative nitrogen or amino acid balance can be reasonably assumed, the existence of normal or high blood levels should not be given particular significance. Amino acid supplementation may make a lot of sense then in situations where it is remains controversial such as with hypertension, kidney disease, dementia, or in relation to covid-19 . Not only do naive correlations prompt futile intervention trials but they may also discourage effective treatment investigations too. Direct intervention and empirical successes need to be seriously considered even when less direct measures conflict. Ultimately well controlled randomized clinical intervention trials with clinical endpoints will have to settle these issues rather than just correlations or associations.

4. SUPPLEMENTAL INFORMATION

4.1. Computer Code

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Appendix A: Statement of Conflicts

No specific funding was used in this effort and there are no relationships with others that could create a conflict of interest. I would like to develop these ideas further and have obvious bias towards making them appear successful. Barbara Cade, the dog owner, has worked in the pet food industry but this does not likely create a conflict. We have no interest in the makers of any of the products named in this work.

Appendix B: About the Authors and Facility

This work was performed at a dog rescue run by Barbara Cade and housed in rural Georgia. The author of this report ,Mike Marchywka, has a background in electrical engineering and has done extensive research using free online literature sources. I hope to find additional people interested in critically examining the results and verify that they can be reproduced effectively to treat other dogs.

Appendix C: Symbols, Abbreviations and Colloquialisms

TERM	definition and meaning
AA	amino acid
AKI	acute kidney injury
BCAA	branched chain amino acid
CKD	chronic kidney disease
CNS	central nervous system
CSF	cerebrospinal fluid
GI	gastrointestinal tract
MAO	monoamine oxidase
RBC	red blood cell
SMVT	sodium dependent multivitamin transporter
TCA	tri-carboxylic acid cycle
URL	uniform resource locator

Appendix D: General caveats and disclaimer

This document was created in the hope it will be interesting to someone including me by providing information about some topic that may include personal experience or a literature review or description of a speculative theory or idea. There is no assurance that the content of this work will be useful for any paricular purpose.

All statements in this document were true to the best of my knowledge at the time they were made and every attempt is made to assure they are not misleading or confusing. However, information provided by others and observations that can be manipulated by unknown causes ("gaslighting") may be misleading. Any use of this information should be preceded by validation including replication where feasible. Errors may enter into the final work at every step from conception and research to final editing.

Documents labelled "NOTES" or "not public" contain substantial informal or speculative content that may be terse and poorly edited or even sarcastic or profane. Documents labelled as "public" have generally been edited to be more coherent but probably have not been reviewed or proof read.

Generally non-public documents are labelled as such to avoid confusion and embarassment and should be read with that understanding.

Appendix E: Citing this as a tech report or white paper

Note: This is mostly manually entered and not assured to be error free.
This is tech report MJM-2021-015.

Version	Date	Comments
0.01	2021-12-20	Create from empty.tex template
0.50	2021-12-22	Release for comment
-	December 22, 2021	version 0.50 MJM-2021-015
1.0	20xx-xx-xx	First revision for distribution

Released versions,
build script needs to include empty releases.tex

Version	Date	URL
0.50	2021-12-22	https://www.researchgate.net/publication/357250784_The_Paradox_Paradigm_When_Could_Amino_Acid_Supplem
0.50	2021-12-22	https://www.academia.edu/s/3b3273469a
0.50	2021-12-22	https://www.linkedin.com/posts/marchywka_amino-acid-blood-levels-versus-production-activity-68794158

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title =”The Paradox Paradigm: When Could Amino Acid Supplements Be Beneficial?” ,
author =”Mike J Marchywka ” ,
type =”techreport” ,
name =”marchywka-MJM-2021-015-0.50 ” ,
number =”MJM-2021-015” ,
version =”0.50 ” ,
institution =”not institutionalized, independent ” ,
address =” 306 Charles Cox , Canton GA 30115” ,
date =”December 22, 2021” ,
startdate =”2021-12-20” ,
day =”22” ,
month =”12” ,
year =”2021” ,
author1email =”marchywka@hotmail.com” ,
contact =”marchywka@hotmail.com” ,
author1id =”orcid.org/0000-0001-9237-455X” ,
pages =” 10”
}

Supporting files. Note that some dates,sizes, and md5’s will change as this is rebuilt.
This really needs to include the data analysis code but right now it is auto generated picking up things from prior build in many cases

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3953 Dec 22 08:16 comment.cut 49a6350413f114d877e997ae0d93535f
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