Release Notes 2021-07-17: : While I tried to make it cohesive, this is a bunch of stuff about fibrinogen dynamics and coagulation optimization. The end result of the math looks right but there may be several mistakes in the few lines of algebra as proof reading may have suffered. Citations are lacking to support many assertions but for the intended audience familiar with the literature it should not present a large concern. It appears that a lot of this is in pieces in older literature but is more relevant today and less mentioned. There may be similar work I missed. This work was furthered by convesations on LinkedIn [12]. **This work elaborates a view on an unresolved issue and is not advice for any specific situation. I am not a doctor or a vet and this has net been peer reviewed,** *comments welcome* **. Caveat emptor.**

Considering Alternative Fibrinogen Fates in Diseased States

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(Dated: July 17, 2021)

Fibrinogen(FGN) dynamics are an important part of cause and effect in coagulopathies but FGN has several possible fates including modifications that can change it's functional characteristics thereby confounding common functional assays. This note considers features of the diseased state, such as reactive environments and reduced hepatic function, that may change concentration and functional activity leading to less intuitive interventions. These ideas are assembled into rate equations demonstrating the possible roles of each effect and importance of clearance times in addition to blood levels. In the diseased state, oxidizing species may segregate and compete with normal clot nuclei allowing normal clots to help sequester the damage if they can grow well. In coagulopathies where diverse anticoagulants mysteriously have limited results, this analysis and results with heartworm positive dogs support a beneficial role for thrombin cleaved FGN and vitamin K.

This note explores limitations of isolated fibrinogen (FGN) assays in resolving coagulopathies and motivates a role for better clotting, possibly requiring more vitamin K. The reader is presumed familiar with the literature and only a few citations are included here to make specific points. One review from 2018 [14] discusses most of the important topics that motivate this work including damaged FGN , disease concerns with hyperfibrinogenemia, paradoxes surrounding cirrhosis or liver function , and related topics such as the impact of cellular inclusions on clot properties.

Hyperfibrinogenemia per se has been proposed as a causal factor in vascular disease but the link is far from clear. One investigation on mice over-producing FGN did find some inconsequential additional fibrin deposition in specific organs and increased D-dimers but no pathological clotting in response to injury and maybe evidence that fibrin enhanced thrombin sequestration occurred in this state [15]. This suggests more clean FGN may be good and the D-dimers reflect normal homeostatic mechanisms. Note too that clearance may saturate and increased blood levels may not clear as quickly as lower ones if hepatic clearance is an active process. Also there is no indication of the vitamin K status of these animals which could change the ratio of fibrin to clotting enzymes such as thrombin. The ferric chloride injury model may have created damaged FGN.

Dysfibrinogenemia, the existence of FGN like molecules that do not perform properly, is indicated by an excessive ratio of antigen or mass to functional amounts resulting in both bleeding and thromosis [7]. It is often thought of as genetic but can be acquired. This source mentions altered post translational modification due to liver disease as one cause but there is no discussion of spontaneous modifications or oxidation related to disease and extended lifetime. The issues with low or dysfunctional FGN including thromboses have been explored [23] and observations support the notion of better clots with more fibrin to help bury the thrombin. Platelets are mentioned but clotting via NET's was not as well elucidated. As with most literature on this topic, the concern is more with genetic diseases than a net result of acquired states.

Measurement of FGN is one step towards understanding the issue and this is typically performed with the functional Clauss method which had been described as the "gold standard for fibrinogen quantification " [11] . This method uses high concentrations of thrombin to clot dilute citrated plasma giving a functional assay that may be contrasted to immunological methods using more direct detection with antibodies [27]. However, it is a challenge to even account for assay interferences such as direct thrombin inhibitors [3] [17] which are not supposed to modify the FGN. There are however meaningful ways for dysfibrinogenemia to decouple concentration from Clauss functional results. In 1995, it was reported that oxidized FGN decreased clotting due to the resulting fibrin monomers inability to polymerize

*Electronic address: marchywka@hotmail.com; to cite or credit this work, see bibtex in Appendix E

[26]. A 2009, report demonstrated that oxidized FGN added to normal plasma increased clotting time [4] suggesting that more FGN would be less functional in some cases. A literature review from 2020 determined some knowledge gaps exist but properties of different modifications had been cataloged [8]. With the exception of acetylation, most modifications in that reviews reduced fibrinolysis of resulting clots implying more likelihood of contributing to occlusive disease. Oxidation could reduce cleavage by thrombin and reduce fiber diameter and permeability while increasing density and crosslinking along with reduced polymerization rate and increased initiation time. These properties may contribute to long lived clots in vivo but may even decrease measured FGN concentrations. (These modified forms could be described as degraded FGN or "fibrinogen degradation products" but this latter term is normally used for the products of clot removal[24].)

Oxidized or modified FGN's have been investigated before [21]. , but even then the Clauss method may be employed [16] with no obvious consideration of the contributions of the modified FGN. A 2017 study in CKD patients described pathological clotting as , " a coagulopathy consisting of delayed clot formation, but increased final clot strength and decreased clot breakdown " [25] which suggests modified FGN which would not be well accounted for in a Clauss assay.

An interesting work from 2000 addressed some of these issues in type 2 diabetes patients demonstrating increased FGN production and turnover and contrasted this to the situation with increased FGN in the elderly but continued to suggest the increased turnover was pathogenic [5]. The current work suggests the opposite issues with turnover and indeed the increased turnover may initially be an adaptive response as the subjects had " no detectable vascular complications" at the time and its not clear how these may evolve compared to other groups.

Thrombin mediated conversion of clean FGN to fibrin produces normal physiological clots that tend to resolve well. The oxidized or non-enzymatic clots which depend on FGN dynamics are likely to be a bigger problem. Rate equations illustrate the problem with two species of FGN : the clean one, FGN_0 which clots normally via thrombin and the pathological derivative FGN_x assumed to create more durable clots much more slowly possibly without the help of thrombin and not significantly adding to the Clauss result. These equations are,

$$\frac{d[FGN_0]}{dt} = A - (C + a_{clot} + a_{mod})\,[FGN_0] \tag{1}$$

$$\frac{d[FGN_x]}{dt} = a_{mod}[FGN_0] - (C + a_{clotX})\,[FGN_X] \tag{2}$$

where A is a synthesis rate determined by the liver , C is a clearance time scale again assumed to be hepatic , and the last two terms are time scales for normal thrombin mediated clotting , a_{clot} , and modification, a_{mod}, for producing the degraded version from the clean one. The modified FGN is similarly removed by the liver and also has a characteristic time scale for forming pathological clots a_{clotX}.

Defining some lifetimes from the time scales,

$$\frac{1}{\tau_0} = C; \frac{1}{\tau_1} = C + a_{clot} + a_{mod}; \frac{1}{\tau_2} = C + a_{clotX} \tag{3}$$

the expressions become more intuitive.

In steady state,

$$[FGN_0] = \frac{A}{(C + a_{clot} + a_{mod})} = A\tau_1 \tag{4}$$

$$[FGN_x] = \frac{a_{mod}[FGN_0]}{(C + a_{clotX})} = \frac{Aa_{mod}}{(C + a_{clot} + a_{mod})\,(C + a_{clotX})} = Aa_{mod}\tau_1\tau_2 = [FGN_0]a_{mod}\tau_2 \tag{5}$$

and total FGN is

$$[FGN] = [FGN_0]\,(1 + a_{mod}\tau_2) \tag{6}$$

.

In the absence of significant modification and clotting,

$$[FGN_0] = \frac{A}{C} = A\tau_0 \tag{7}$$

The gross rate of pathological clotting, G, is then,

$$G = [FGN_x] * a_{clotX} = \frac{A a_{mod} a_{clotX}}{(C + a_{clot} + a_{mod})(C + a_{clotX})} = [FGN_0] a_{mod} a_{clotX} \tau_2 = \frac{[FGN] a_{clotx} a_{mod} \tau_2}{1 + a_{mod} \tau_2} \quad (8)$$

G decreases with increasing normal clotting rate but the behavior depends on which terms dominate the time scales τ_1 and τ_2. In a state of health, presumably τ_1 and τ_2 are dominated by C,

$$G \approx \frac{[FGN] a_{clotx} a_{mod}}{C + a_{mod}}; G \approx \frac{[FGN_0] a_{clotx} a_{mod}}{C} \quad (9)$$

.

and when the modification time is slow compared to clearance, the gross pathological clotting is related to FGN and hepatic clearance rate or C^{-2}. In the other extreme, where hepatic clearance C is much smaller than the other sinks the FGN lifetime is dominated by the modification and clotting terms,

$$\frac{1}{\tau_1} \approx a_{clot} + a_{mod}; \frac{1}{\tau_2} \approx a_{clotX} \rightarrow G \approx a_{mod} [FGN_0] \approx \frac{[FGN] a_{mod} a_{clotx}}{(a_{clotX} + a_{mod})} \quad (10)$$

and the relative amount of the two FGN species is determined by the ratio of a_{clotX} and a_{mod} or the deposition and modification coefficients. With

$$[FGN_0] \approx \frac{A}{(a_{clot} + a_{mod})} \quad (11)$$

more physiological clotting can reduce FGN as long as it can be made competitive with modification.

Depletion of clotting factors or consumptive coagulopathy is a well known problem but facilitating thrombin derived clots may not be considered when the apparent problem is hypercoagability. Further, the contribution of liver function may be forgotten both in chronic situations with older people and acute disease related problems with elevated liver enzymes. For example, see [10].

Previously vitamin K had been discussed for treatment of covid-19 [13] [1] [18] with precedent for usage in cases where anti-thrombotics may be used such as heartworm positive dogs [19]. The apparent paradox could be understood in the static case with a non-monotonic activity-response curve for vitamin K [20] with only marginal concern for increased trigger densities or other components. This work adds rate equations relating pathological clotting to slow normal clotting that further motivate the vitamin K approach . The covid-19 coagulopathy has been characterized by elevated PT and APTT simultaneous with elevated FGN and D-dimers [2]. This may be explained by high clot turnover along with consumptions of other clotting factors with greatly increased synthesis of FGN but is also consistent with reduced liver clearance of FGN and D-dimers. The activated immune system normally described with covid-19 along with elevated liver enzymes suggests reduced clearance and more oxidation of FGN. Solid evidence of vitamin K deficiency does not exist yet but in one small study, proteins C and S tended to be lower in ICU covid-19 and non covid-19 patients [6] although significance of the difference was not suggested in the work which compared covid-19 to others. Another study of 12 covid-19 ICU patients demonstrated some tendency to be towards the low normal end for both proteins C and S [9]. Reference ranges however may need further examination and carboxylation status of thrombin may need to be measured.

In the presence of extended FGN hepatic lifetime τ_0, decreased C in the above rate equations, and an oxidizing environment around areas of immunological activation, clearance of FGN through thrombin may be a reasonable approach among feasible alternatives. It may not be possible to raise physiological clotting rate fast enough to remove enough FGN before it converts to a pathological clot but it may help. Homeostatic mechanisms could also increase "A" in response to these efforts as well as disease. With the identification of FGN oxidation products that may produce lysis resistant clots and not contribute to the Clauss assay, it becomes important to reconsider all the "obvious" notions especially as these interventions fail. While this model is highly simplified, it may also be worth noting that other specific means of FGN cleavage exist, such as those related to pathogens [22], for which complete inhibition may not be beneficial unless combined with thrombin derived clots. Finally, it's possible that many triggers for normal coagulation exist in the reactive environment modifying the FGN and a normal clot may be able to help bury some of those similar to proposed thrombin sequestration.

1. SUPPLEMENTAL INFORMATION

1.1. Computer Code

2. BIBLIOGRAPHY

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Acknowledgments

1. Pubmed eutils facilities and the basic research it provides.

2. Free software including Linux, R, LaTex etc.

3. Thanks everyone who contributed incidental support.

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

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 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-2021-006.

Version	Date	Comments
draft	2021-07-08	approximate date of drafts/fibrinogen
0.01	2021-07-17	Create from empty.tex template
0.5	2021-07-17	email to Gerald Haug
0.5	2021-07-17	post on academia.edu
-	July 17, 2021	version 0.50 MJM-2021-006
1.0	20xx-xx-xx	First revision for distribution

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

Version	Date	URL
0.50	2021-07-17	email to Gerald Haug
0.50	2021-07-17	https://www.academia.edu/s/4549820b65

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AUTHOR = {M.J. Marchywka},
TITLE = { Considering Alternative Fibrinogen Fates in Diseased States},
NUMBER = {MJM-2021-006},
VERSION = {0.50 July 17, 2021 PUBLIC NOTES },
INSTITUTION = { not institutionalized , independent},
ADDRESS = {306 Charles Cox , Canton GA 30115},
NOTE = {Version 0.50 , may change signficantly if less than 1.00 },
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DAY = {17},
MONTH = {7},
YEAR = {2021},
AUTHOR1EMAIL = {marchywka@hotmail.com},
AUTHOR1ID = {orcid.org/0000-0001-9237-455X},
PAGES = { 7 },
CONTACT = {marchywka@hotmail.com},
FILENAME = {fgnrates}
}

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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51036 Jul 17 10:48 ./fgnrates.bib bf719f478f4035519167cc338e6ab024
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31050 Jul 21 2011 /usr/share/texlive/texmf-dist/bibtex/bst/urlbst/plainurl.bst
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