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The Multiple Sclerosis Stress Equation

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Abstract

Background: Multiple Sclerosis (MS) is an auto immune disease, unpredictable in its symptoms, with uncertain prognosis. The most common phenotype is Relapsing-Remitting (RRMS). Despite remissions, relapses lead to CNS damage, and less CNS function recovery from recurrence of relapses, leading to increasing debilitation. There is no cure, and medicines are used for prevention of relapse, with intervention reserved generally for relief from serious inflammatory symptoms.

Methods: This statistical study examines a 7-year span of very detailed medical records of one RRMS patient. Seven clinically observable MS disease responses to distress are identified by mapping the magnitude of distress against duration of symptom sets. Natural divisions were identified in this mapping. Probability distributions, within these natural divisions, were formally constructed. Further investigation is warranted as to how these relate to physiologic, histologic, and biochemical processes involved in MS pathology.

Results: This study establishes that stressors exacerbate and expose the presence of the disease and that distress, is the missing consideration in many clinical studies as it is an intermediate outcome between stressors and symptoms. The statistical analysis documents 4 distress characteristics, and 7 Disease Response characteristics. Distress or its absence can predictably induce an MS relapse or remission, respectively. Mathematical and statistical models between distress and relapse are derived that characterize the RRMS disease response. These formulae facilitate managing other patients' symptoms. This study recommends several approaches to modeling symptom set data for the purpose of yielding better, more consistent models. For example, how to utilize the results of survival functions, and EDDS. A Stress-Disease Meta Model is proposed. That, Stressors cause Susceptible patients to exhibit a Stress Response (or distress) that leads to Effectors causing tissue Injury evidenced as Disease Responses. The Disease Processes determine how healing and/or deterioration is evidenced in the disease as Disease Responses. This facilitates the structuring and tracking of triggers, symptoms, other factors and/or comorbidities, to yield more usable data for statistical analysis. Finally, a multi-process disease-wellness approach is proposed that should open further avenues for research.

Conclusion: MS is considered an unpredictable disease because (1) MS symptom sets are triggered within 3 days of stress triggers, (2) The random arrival of stress triggers causes the appearance of random symptom sets, and (3) MS is also unpredictable as the underlying disease processes are dynamic processes that keep switching.

Keywords: Autoimmune, Demyelination, Relapsing-Remitting, Central Nervous System, Oligodendrocytes, Stress

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Introduction: Overview

Multiple sclerosis (MS) is a chronic autoimmune [1], inflammatory neurological disease of the central nervous system. Prognosis is often uncertain [2]. A management methodology based on stressors is proposed for MS.

It is generally agreed that MS is due to demyelination of the neurons. From a clinical perspective four [3] disease phenotypes are recognized, (i) Clinically Isolated Syndrome (CIS), (ii) Relapsing-remitting MS (RMS), (iii) Secondary progressive MS (SPMS), (iv) Primary progressive MS (PPMS). Even though pathologically there are four fundamentally [4] different patterns of demyelination, it is traditionally viewed [5] as a two-stage disease, with early inflammation responsible for relapsing–remitting disease and delayed neurodegeneration causing non-relapsing progression. The final effectors of demyelination [6] are the microglia, but the initial trigger that leads to abnormal microglial activation is unknown.

The cause of MS is unknown. It is considered to be an autoimmune [1] disease. Research agrees that genetic predisposition, infectious mononucleosis with chronic EBV, vitamin D deficiency and environmental interactions are risk factors for MS. Other Viral [5] and other etiologies and risk factors [7] have also been hypothesized and studied such as infections, vaccines, parasites, solvents, cigarette smoking, body mass index, alcohol & caffeine, the gut microbiota–brain axis, and comorbidities. Research has even considered a fungal etiology [8]. Stress has been increasingly investigated [9-11] as a factor that can be modified and thus affect the course of the disease.

This paper mathematically establishes the effect of stress as a direct cause of MS relapses in RRMS, with applicability to other MS phenotypes. A data-gathering methodology is evaluated. It provides better data for statistical and mathematical analysis of MS and for derivation of more predictive relationships between MS disease pathology and distress.

Results: Summary of Findings

This paper establishes extreme-negative-emotional-stress-response ("distress") as a direct effector of an MS relapse. A data-gathering methodology is evaluated, that provides better data for statistical and mathematical analysis and derivation of more predictive relationships between MS disease pathology and its effectors. A direct relationship between distress and the exacerbation of MS is provided and modeled mathematically, to produce an MS stress equation. It is shown that the exacerbation of MS by distress is predictable and can be expressed mathematically.

The effect of psychological stress on the immune system and disease is established in the literature [9-11], including correlation of stress with the onset and exacerbation of MS. The present study shows that the occurrence of distress can be regarded as a trigger, and each distress trigger will induce an MS symptom set. A symptom set is defined as a set of one or more symptoms typical for MS, and the manifestation of the symptom set depends on where the demyelination occurs in that patient, and to what extent. Typically discussed examples of symptoms in MS could include increased fatigue, balance problems, degradation of coordination, cognitive problems, vision problems, frequent urination and bowel incontinence, hearing problems etc.

As previously reported [2] patient perspectives on disease progression in MS and other chronic progressive conditions are under-investigated and under-reported. The limited evidence available highlights the importance of providing adequate information and effective communication involving healthcare professionals [2]. There is the need to structure the clinical observations into characteristics that lead to more effective communications. Towards this goal, **Figure 1** summarizes the statistical processes that govern the relapse and remissions with respect to symptom sets and stress triggers using the Hazari Data Set (see next section). Herein, relapse is defined as the onset or exacerbation of one or more symptom sets.

This study proposes subtle shifts in our perspective towards MS research that emerges from studying the effect of acute and chronic stressors on MS symptom sets.

This paper proposes (i) the statistical and mathematical properties of MS symptom sets and the role of distress triggers (ii) an MS Stress-Disease Meta Model that is a step-by-step cause and effect sequence structure for directly relating distress and the progress of MS and (iii) other inferences pertaining to disease analysis.

The Stress-Disease Meta Model consists of 8 parts,

1. Susceptibility: A measure between 0 (will not succumb to the disease) and 1 (will always succumb to the disease). It is an indication of how likely the underlying tissue is likely to suffer injury in the presence of stress responses and/or effectors. This is not easy to estimate. As a population sample, susceptibility can be measured as a probability or proportion of the population that experience the disease. That is, population susceptibility is not conditional on the presence of Stressors or Stress Response. However, as an individual, there likely will be genetic, and environmental factors that condition susceptibility. A mathematical definition of susceptibility is outside the scope of this paper.
2. Stressors: Cause the disease to be exposed or made visible in susceptible patients when these stressors produce harmful stress responses. This is represented as distress triggers in our stress equations.
3. Stress Response: Indicates how the biochemistry responds to stressors. This is a very complex process, and our analysis suggests that these complex processes involve control mechanisms that are both feedforward and feedback. These control theory concepts are well documented in electrical engineering. Feedforward is a mechanism to control outcomes by knowing the environment, while feedback is a time delayed mechanism to achieve stability within that environment. In a sense one could say that

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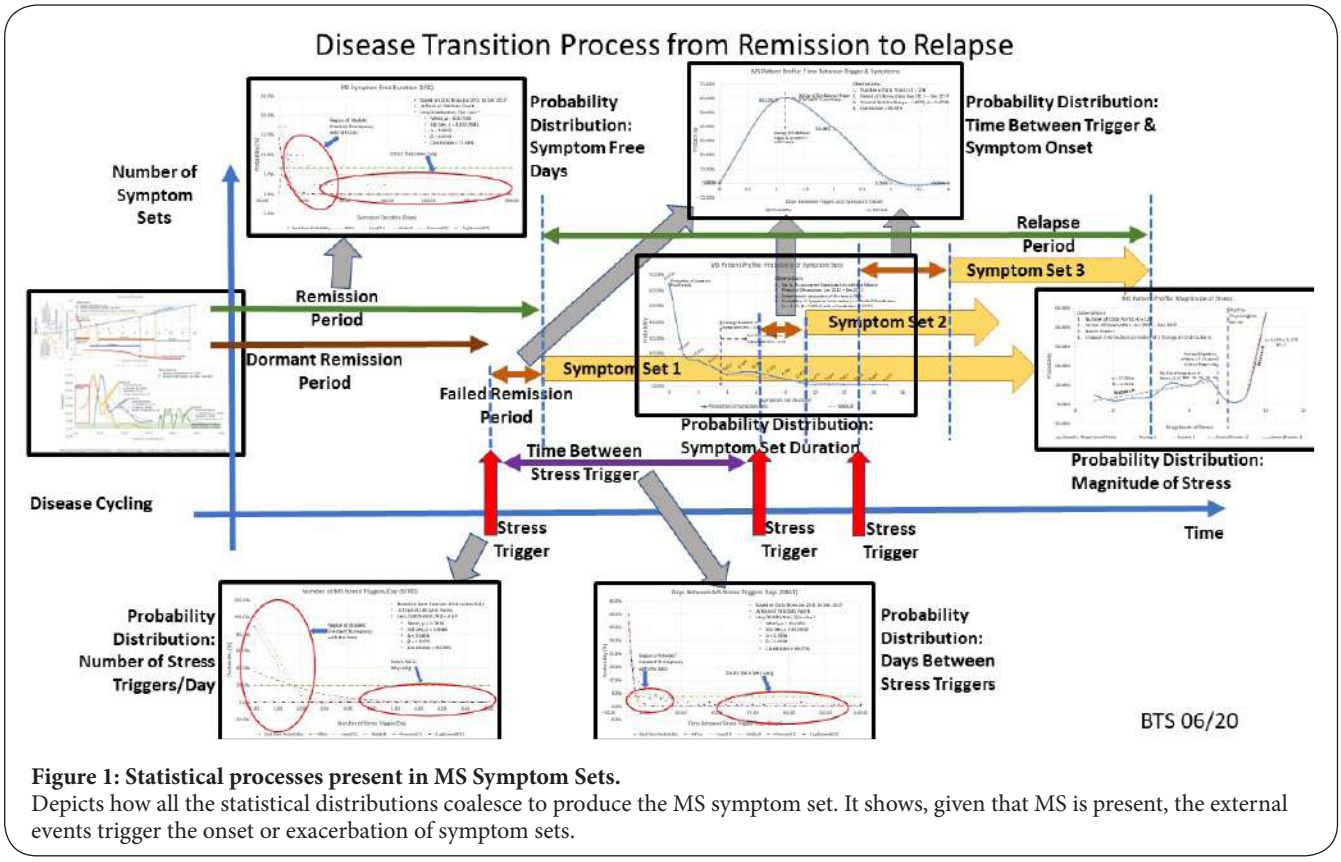

Figure 1: Statistical processes present in MS Symptom Sets.
Depicts how all the statistical distributions coalesce to produce the MS symptom set. It shows, given that MS is present, the external events trigger the onset or exacerbation of symptom sets.

a drug-based treatment is a feedforward mechanism, while symptom management is a feedback mechanism. This paper has not made any attempt to mathematically introduce these control mechanisms as these are outside the scope of this paper.

4. Effectors: The mechanism (toxins, virus, etc.) by which stress response leads to susceptible tissue injury.
5. Injury: Damage done to susceptible tissue, including both temporary and permanent damages.
6. Disease: A state of being in injury.
7. Disease Response: The statistical behavior of injured tissue exhibiting as a disease.
8. Disease Processes: The pathogenesis and biochemistry that describe individual, connected sequences to injure or heal the affected tissue. There are two classes of Disease Processes,

a. Regeneration Process: A group of subprocesses that heal the injured tissue.

b. Degeneration Process: A group of subprocesses that cause injury to tissue.

Our study determined that an MS patient, Susceptible to Stressors, has predictable Stress Response - Disease Responses relationships. **Table 1** demonstrates that application of harmful-stress, triggers distress. This in turn leads to the onset or exacerbations of MS symptom sets within 3 days. The literature provides evidence that these symptom sets can be strongly associated with brain lesions [**12**,**13**]. This deterministic Stress Response may explain the inconclusiveness or negation of some earlier research [**14**-**17**] as the precedent step, distress, was not sufficiently or uniquely accounted for.

This paper reports the results of the investigation into how distress induces MS symptom sets [**18**-**20**], documents the probability distributions characteristic of the disease, proposes several new statistical responses correlated with symptom production, and establishes that distress does induce MS symptom sets. The scope of the paper does not include the pathology of the Stress Response resulting in the inducement or action of Effectors, or of Disease Processes leading to Injury. However, the mapping of the statistical characteristics of the Disease Response to Disease Processes warrants future study.

The analyses of **Tables 1 (a)** & **(b)**, shows that:

1. Stress Not Present (**Table 1(a)**, 3rd & 4th row): MS symptoms are not induced without negative stress.
2. Stress Present (**Table 1 (b)**, 1st & 2nd row): Negative stress induces MS symptoms.

a. 109 (78.4%) out 139 days, the presence of negative stress (Stress Magnitude ≥1) results in an increase in the number of symptom sets.

b. 2 (1.4%) out of 139 days, symptoms continue to be present but at some point, in the future (1 and 280 days), the

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Table 1: Day Count & Magnitude Per MS Condition.

Change in Number of Symptom Clusters		Increase	Increase	Increase	No Change	No Change	No Change	Decrease	Decrease	Decrease	
Change in Symptom Cluster Duration		**Increase**	**No Change**	**Decrease**	**Increase**	**No Change**	**De-crease**	**Increase**	**No Change**	**Decrease**	
Triggers	**Negative Stress Magnitude**										**Totals**
Yes	>0	21	73	15	0	2	0	7	7	4	129
Yes	=0	0	0	0	0	8	1	0	1	0	10
No	>0	0	0	0	0	0	0	0	0	0	0
No	=0	22	11	47	91	2042	111	53	32	14	2423
	Totals	43	84	62	91	2052	112	60	40	18	2562

Table 1(b)

Change in Number of Symptom Clusters		Increase	Increase	Increase	No Change	No Change	No Change	Decrease	Decrease	Decrease	
Change in Symptom Cluster Duration		**Increase**	**No Change**	**Decrease**	**Increase**	**No Change**	**De-crease**	**Increase**	**No Change**	**Decrease**	
Triggers	**Negative Stress Magnitude**										**Aver-age**
Yes	>0	7.4	7.5	8.1	--	5.5	--	8.1	8.4	5.8	7.5
Yes	=0	--	--	--	--	0.0	0.0	--	0.0	--	0.0
No	>0	--	--	--	--	--	--	--	--	--	
No	=0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Average	3.6	6.5	2.0	0.0	0.0	0.0	1.0	1.5	1.3	0.4

number of symptom sets remains the same.

c. In the remaining 18 (12.9%) days, symptoms continue to be present but at some point, in the future (1 and 280 days), the number of future symptom sets decrease.

d. When no stress is present 10 (7.2%) out of 139 days, at some point, in the future (1 and 280 days), the number of future symptom sets decrease or continue with no change.

Table 1 (b) shows that the average Magnitude of Stress was consistent across the 2011-2017 period. This indicates that the stress scoring method was robust.

This paper describes the 7 statistically identified disease responses (A1, A2, B, IR, NR, NT & U) that are present with MS symptom sets and their associated statistical properties. This paper does not report how distress, alters brain neurology, as that would require regular testing, such as weekly MRI scans. However, even with MRI scans it has been shown that intracortical lesions remain largely undetected with current MR imaging resolution [5].

MS is known as an unpredictable disease [6]. It has been shown that stress management can reduce [21-24] certain types of brain lesions. Therefore, the understanding of the statistical properties of these negative-stress-triggers, is necessary to manage subsequent MS symptoms. Otherwise, without this understanding, MS may present as different variations of the same underlying disease. Histologically [3] most cases exhibit T-cell and macrophage-dominated inflammatory reaction, even though there may be different versions of the disease. This paper proposes that MS exhibits many different clinical variations because of the different statistical properties of negative-stress-triggers. Therefore, it can be hypothesized that stress arises as a product of the onset or exacerbation of an MS symptom set, or pursuant to it, which consequently acts as a feedback mechanism to modify the exacerbation and affect the course of the disease.

Though the cause of MS is still inconclusive [6] (and a cure is not yet within reach), this paper proposes a management of symptom sets based purely on statistical inferences. This is because distress does have a physiological impact on the body that triggers the onset and exacerbations of MS symptom sets, and knowledge of the Disease Response to the Stressors can be used to establish the criteria for disease management.

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Given that this study has confirmed, **Table 1**, that negative-stress-triggers cause the onset and exacerbations of MS symptom set, to manage this, this paper proposes,

1. Trigger Identification: It is imperative that the stress triggers be identified. These stress triggers were found to be within 1 to 3 days (short duration confirmed in the literature [**20**]) of the start of a symptom set, and therefore, can be identified by searching the immediate recent past for possible causes.
2. Stress Management [**25**,**26**]: Stress-trigger buffers, be identified and implemented. That is, mechanism to deflect, intervene, lessen, or eliminate negative-stress-triggers together with supportive and therapeutic resources be readily accessible to the patient.
3. Treatment Opportunity: There is a 1-to-3-day gap between negative-stress-trigger events and the start of symptom sets. This 1-to-3-day gap is a specific time-window of opportunity to evaluate early treatments before the start of symptom sets.

Methods: Mathematical & Statistical Models

The MS mathematical models reviewed here illustrate how the statistical study presented in this paper is different from these models, and therefore, provides new avenues for further research.

The Simple Mathematical Model [**27**] (SMM) for relapsing remitting multiple sclerosis was proposed to explain the non-linear irregular clinical cases and disseminated distribution of the lesions in MS with either immune or viral harmful effectors. Relapsing Remitting Multiple Sclerosis Model [**28**] (RMSM) based on SMM was proposed as a time dependent version of the SMM and assumes that the affected nerve cells secrete the toxic effectors (virus) which invade the robust nerve cells. The Reaction-Diffusion-Chemotaxis Model [**29**] (RDCM) proposes three equations describing the evolution of macrophages, cytokine, and apoptotic oligodendrocytes in the dynamics of multiple sclerosis.

All three mathematical models are different from this paper's findings. This paper has shown that when MS is present, negative stress, triggers negative emotions which in turn triggers MS symptom sets observed clinically. Whereas SMM, RMSM & RDCM are concerned with modeling the underlying disease manifestation but not related to symptom sets. Building [**27**] a reliable mathematical model to reproduce the clinical manifestation in MS is one of the possible approaches to elucidate the pathophysiological mechanism of MS to invent further therapeutic approaches. The first two uses some form of the Reproduction Model. One of the authors, Solomon, proposed Collated Distributions [**30**] and Wilcoxon Regression [**31**] as more robust statistical techniques to modeling non-linear functions. Noting that many commonly used statistical techniques require Normality, the standard references [**32**] would have been better if it covered more ground on the cautions of statistical analyses.

However, there are two other models [**33**,**34**] worth critiquing. One of the models [**33**], as will be shown later, does not distinguish between Stressors and Stress Response. The other model [**34**], is a much better model in that it provides useful insights into the MS disease. However, one of the authors, Solomon, is wary of polynomial models [**27**-**29**,**33**] as polynomials can be made to fit any data without sufficiently explaining the what, or the why of the underlying process. Note that, this paper references the Levy Distribution [**31**] which is the range-constrained Power Law distribution with lower L and upper U bounds from the data x, $L < x < U$ (unlike the Power Law where the data is unbounded $0 < x < \infty$) and yields different statistical properties from the unconstrained Power Law. For the Weibull Distribution the shape & scale parameters are α & β, respectively.

Methods: The Hazari Data Set

Patient Hazari is a research scientist diagnosed with relapsing-remitting Multiple Sclerosis. Intent on understanding and managing his disease, he collaborated with his doctors by keeping detailed medical records with the goal of using empirical findings in conjunction with treatments to minimize relapses and symptoms. Empirically, he determined a correlation between distress and relapse, and developed and used stress management methods.

The Hazari data, records with daily granularity, the symptoms when present, of his MS relapses such as numbness in extremities, bladder and bowel dysfunction, visual disturbances, muscle recruitment, but also identifies imaging findings, such as new findings in his brain and spine MRIs.

The distress triggers in the study time window of 2010-2017 originated from two sources and were inflicted as sudden and transient, or sustained for a short time, but with protracted effect. During this period, he actively managed his disease in response to acute and chronic stress. Hazari's medical records document multiple parameters, date & stress triggers ratings, with fine granularity. His symptoms were tracked by date. Thus, it is possible to statistically correlate the effect of distress triggers with symptoms. Symptoms were associated into one set if they are discerned within 48 hours of one another, except if another stress trigger is present in that time.

Stress triggers were assigned magnitudes from 0-10, with 10 indicating the most severe emotional distress described as equivalent to causing the death of a loved one. Stress triggers that did not elicit distress were assigned a value of 0. All trigger magnitudes from 1-10 produced symptom sets that persisted more than 48 hours. All stress data below magnitude 1 is excluded in this paper.

The threshold of 1 was met by distress that resulted immediately in mental and physical effects including feeling very hot and sweating, elevated pulse rate and blood pressure, feeling of weight on his chest and burning in his stomach and at the base of his sternum, feeling alarm, fear or anger, significant mood change, hopelessness, lingering anxiety,

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showing uncharacteristic reactivity, and loss of concentration associated with pre-occupation with the trigger. These responses would have to be coupled with ensuing frequent distraction by thoughts about his distress, and other observations including increased incidence of mistakes or accidents, loss of focus, inability to sleep, pre-occupation with the trigger and the perception that he faces a serious problem that is unavoidable and unsolvable, and an inability to cope. These reactions must endure for a minimum of 24 hours from the application of the stress trigger.

An example of a qualifying stress trigger would be hearing news of the MS diagnosis of Hazari's sister on the day she lost her sight. This problem was unavoidable and unsolvable (MS has no cure), and Hazari was unable to cope even if he switched between problem-focused (changing source of stress) and emotional-focused (wishful thinking, distancing, avoiding, positive reappraisal) coping strategies [**35**]. He was very distressed by his sister's diagnosis. Thus, stress magnitudes below 1 indicate the range of all other life and work stressors excluding the exceptional stressors (which meet the threshold qualifying criteria).

In assigning a value to the magnitude of the stress trigger on a Rasch-like scale, Hazari used systematic rating together with retrospective re-adjustment rating. In his rating, he leveraged POMS [**36**], COPE [**37**] and BHS [**38**] for systematic rating over time. Depressive and anxiety symptoms were included to establish convergent validity, given the substantial overlap between these variables and perceived stress noted in the literature [**39**]. Hazari leveraged SDS [**40**], BDI-II [**41**] and HDRS [**42**] for depression and leveraged BAI [**43**], HAM-A [**44**] and SAS [**47**] for anxiety. Coping is an individualized factor [**45**], and illness perception is feedback that increases stress [**46**]. Re-assessment included evaluation of the symptom and disability impact on himself because of the discrepancy between psychological adaptation and biological deterioration, as well as review of the severity of distress after the initial impact. His re-assessment rating leverages QuAT-MS's 12 categories [**36**] and SIP-68 [**48**], PSS [**39**,**49**] (looking back to the trigger date generally within 5-10 days not one month), and CHIP [**49**]. Attention to his deterioration justified the burden of the lengthy characterization.

Three are three parts to stress [**50**],

1. Stressors: Changes/stimuli from the environment that cause "stress".
2. Stress Response: The physiological and psychological responses to those stimuli.
3. Chronic Stress Response: The disease that result from an over stimulation of the physiological and psychological responses. Herein the term Disease Symptoms is used instead of Chronic Stress Response and facilitates the differentiation between acute and chronic disease symptoms.

This paper's investigation is limited to approximately 7 years of this patient's record (2011-2017), containing sufficient trigger-response data for quantitative analysis. These include the distress (Stress Response), and the MS symptom sets (Disease Symptoms). These are then refined down to a window of 2,561 days suitable for statistical evaluation.

The Hazari data was analyzed from a purely statistical point of view with no medical inferences or assumptions to determine the relationships between stress triggers and relapses, as a "black box", and without etiologic or pathologic inferences. The statistical analysis followed a step-by-step methodology to (i) structure the data, (ii) determine the characteristics of the probability distributions present in this structured data, (iii) identify threshold(s) when present and (iv) infer individual disease responses underlying the transformation of stress to MS symptoms.

Methods: Approach & Data Structuring

Boruta, Horvath and MacKellar provided care to Hazari as primary doctors with many other doctors and specialists. As Hazari is a sophisticated professional, he kept detailed daily records of his Multiple Sclerosis disease progression. These records are corroborated by medical records of his doctors. Hazari had not mathematically or statistically analyzed his data prior to Solomon's 2020 analysis, which minimizes any form of confirmation, rejection or recall bias [**51**,**52**].

The approach taken was to first examine the data only from a statistician's point of view with no medical inferences or assumptions. This posteriori data approach leads to the determination of unbiased physical processes which can then enhance the a priori medical knowledge. This is equivalent to knowing what you see versus seeing what you know [**53**]. However, the interplay between the two is what advances the sciences.

Given a very sophisticated and complex health-disease relationship, it is insufficient to just determine parameter values of interest, but to determine the underlying statistical distributions, the disease responses, that are indicative of these disease processes. However, it is not within the scope of this paper to determine what these disease processes are.

Thus, the purpose of data & statistical analyses was to determine identifiable responses that would advance medical research in MS. This requires a careful step by step methodology to (i) structure the data, (ii) determine the characteristics of the probability distributions present in this structured data, (iii) identify threshold level, if and when present, and (iv) infer individual responses or processes underlying the transformation of stress to MS symptoms.

Structuring the data results in the following fields (i) Date of Stress Trigger, (ii) Number of Stress Triggers/Day and up to 6/day were recorded. Out of the selected 2,561-day period, 1,640 (64%) days were symptom free and the remaining 921 (36%) days were not. Distress-triggers were recorded on 139 of these days. (iii) Magnitude of this Distress which ranges between 0 to 10. A zero means that a trigger event did not lead to distress. (iv) Symptom sets, a set of symptoms

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experienced after each trigger event. The advantage of using symptom sets as opposed to symptoms is that symptom sets are less sensitive to sampling errors, and therefore a much more robust measure of symptom duration. Symptoms are induced mostly within 48 hours of a trigger, sometimes within 24 hours and occasionally within 72 hours. Symptom sets in the selected date range could last between 2 and 47 days.

The Hazari data can be divided into (i) Characteristics of Distress and (ii) Clinical Characteristics of MS Stress Response.

Note that the Change in the Symptom Set Duration (Change in Duration) is defined as the difference between the duration of the next Symptom Set and the duration of the current Symptom Set caused by the Stress Trigger.

Findings: The 4 Statistical Characteristics of Distress

In terms of the Stress-Disease Meta Model, this section describes the properties of the Stressors (1. & 2. below) and Stress Response (3. & 4. below) that led to tissue injury and symptom sets. **Table 1** confirms that without these distress-trigger events, there are no symptom onsets or exacerbations. Even though distress is an external factor to MS, it is important to model distress to determine its effects on MS. The operating characteristics of these distress-triggers, provide an understanding of the clinical observation of the onset and exacerbations of MS symptoms. There are 4 negative Distress Mechanisms:

Distress Triggers/Day:

Figure 2 shows that distress triggers/day S_T are Weibull Distribution (α = 2.5416, β = 1.1355). However, a mode of 5 and 6 distress triggers/day exists that belong to a different population of triggers. That is, even though the source of these distress triggers is the same, there exists 2 different originating motivations for these triggers, and therefore care is required when reviewing distress data.

$$P(S_T) = \frac{\alpha}{\beta^{\alpha}} {S_T}^{\alpha-1} e^{-\left(\frac{S_T}{\beta}\right)^{\alpha}} \quad where\ \alpha = 2.5416, \beta = 1.1355 \qquad (1)$$

Time Between Distress Triggers:

Figure 3 shows the Time-Between-Distress-Triggers. This new Levy probability distribution function is the best fit, as the Binomial, Poisson, Weibull, LogNormal, Normal & Beta distributions do not provide even a semblance of a good fit. This Time-Between-Distress-Triggers probability P(T) density function takes the form αT^{β} where T is the duration between triggers with α= 1.7441, β = -1.2560.

$$P(T) = \alpha T^{\beta} \,|_{L=1}^{U=136} \quad where\ \alpha = 1.7441, \beta = -1.2560 \qquad (2)$$

Patient's Response to Distress Magnitude:

Figure 4 documents the probability distribution of the magnitude (on a scale of 1 to 10) of the patient's response to distress, between 2011 to 2017. It is consistent over a 7-year period. This graph shows that there are 2 active responses, A & B. This paper does not address the mapping of these responses to research findings of diseases processes, but this subject is of interest. Disease Response A is active when distress magnitudes S_E are 7 or less and Disease Response B when S_E greater than 8.

$$P(A|S_E) = 0.0166 S_E \,|_{1 \le S_E \le 7} \qquad (3)$$

$$P(B|S_E) = 0.4252 S_E - 3.7795 \,|_{8 \le S_E \le 10} \qquad (4)$$

Where S_E = magnitude of distress, which ranges from 1 to 10. $P(A|S_E)$ and $P(B|S_E)$ are the probabilities of Disease Response A and B given that a negative stress trigger S_T is present.

Psycho-Physiological Threshold:

The data (**Figure 4** vertical purple dashed-line) suggests that there exists a buffering mechanism, that substantially protects the patient from experiencing the largest magnitude of distress which could be labeled as trauma. Herein, this is denoted as the Psycho-Physiological Threshold (PPT). However, when this threshold is breached it results a perceived severe stress of magnitude 9 & 10.

$$PPT = 8 \qquad (5)$$

The probability distributions of **Figures 2** & **3** strongly suggest that the source of the distress triggers was not a random process, as random arrivals obey a Poisson Distribution and the time between random arrivals obey an Exponential Distribution. Neither are true in this case.

FINDINGS: The 7 Clinical Statistical Characteristics of MS Disease Response

This section covers Disease Responses of the Stress-Disease Meta Model, that is, the statistical properties of Responses (symptom sets) given that Injury is present. Susceptibility, Effectors, and Injury require pathogenesis investigations that are not within the scope of this paper.

A symptom set is a set (at least one or more) of symptoms observed between a symptom set Start Date and a symptom set End Date. Multiple symptom sets were recorded concurrently, each with their own start and end dates. Note that, a subsequent symptom set consists of symptom onsets and/or exacerbation of previous symptoms. The Hazari Data Set shows that there can be as many as 15 concurrent symptom sets (**Figure 5**). Symptom sets provide a higher resolution of the MS disease characteristics than just Relapse Periods would. Similarly, individual symptoms would provide a higher resolution than symptom sets. However, individual symptoms have not been reviewed for this paper. Note that, the parameters α & β of the statistical models presented in this section may be patient dependent.

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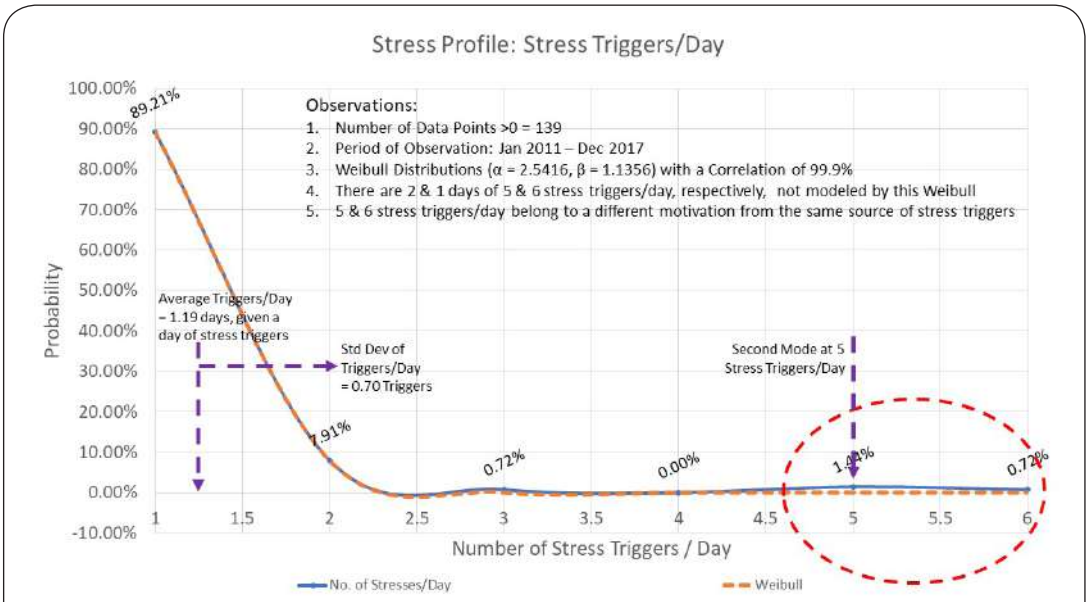

Figure 2: Stress Profile: Stress Triggers/Day between Jan 2011 to Dec 2017.
External Triggers: Probability distribution of number of stress triggers experienced per day by this patient when stress triggers are present. On average this patient experienced 1.19 stress triggers per day.

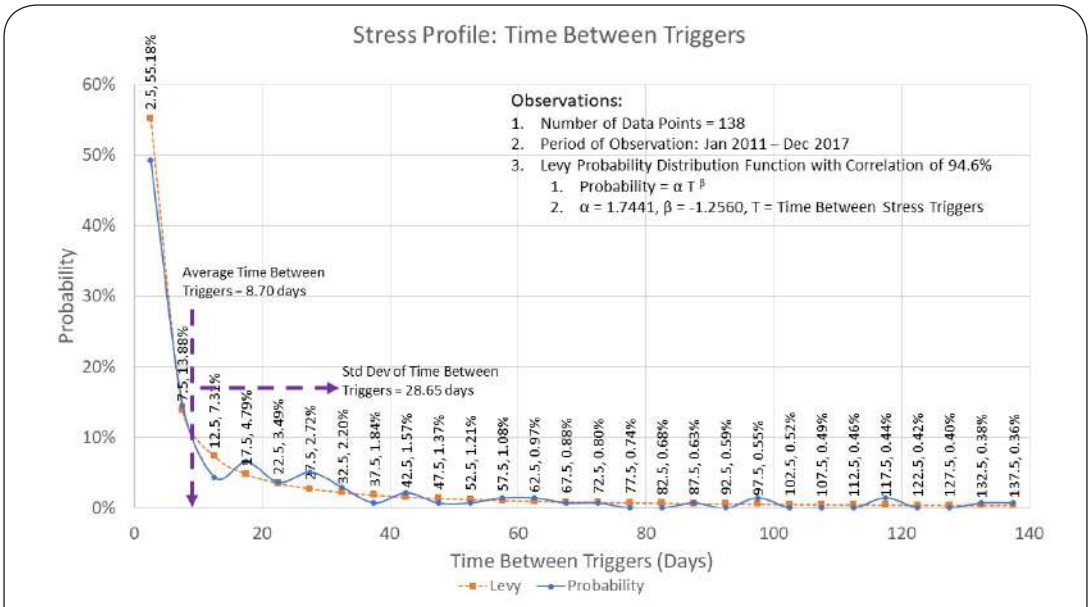

Figure 3: Stress Profile: Time Between Stress Triggers between Jan 2011 to Dec 2017
External Triggers: Probability distribution of the time, in days, between stress triggers experienced by this patient. Over the 8-year period this time between triggers obeys a Levy Distribution.

The Hazari Data Set shows that MS can be statistically characterized by 7 properties that describe the statistical properties of relapses and remissions given that stressors are in effect, and that there are in total 7 disease responses A1, A2, B, IR, NR, NT & U.

Relapse Period:

Figure 5 shows how a Relapse Period can be deconstructed into symptom sets S_C. Therefore, a Relapse Period is defined as Start Date of the first symptom set to the End Date of the last symptom set.

The probability $P(N_C|S_C)$ of N_C symptom sets S_C given

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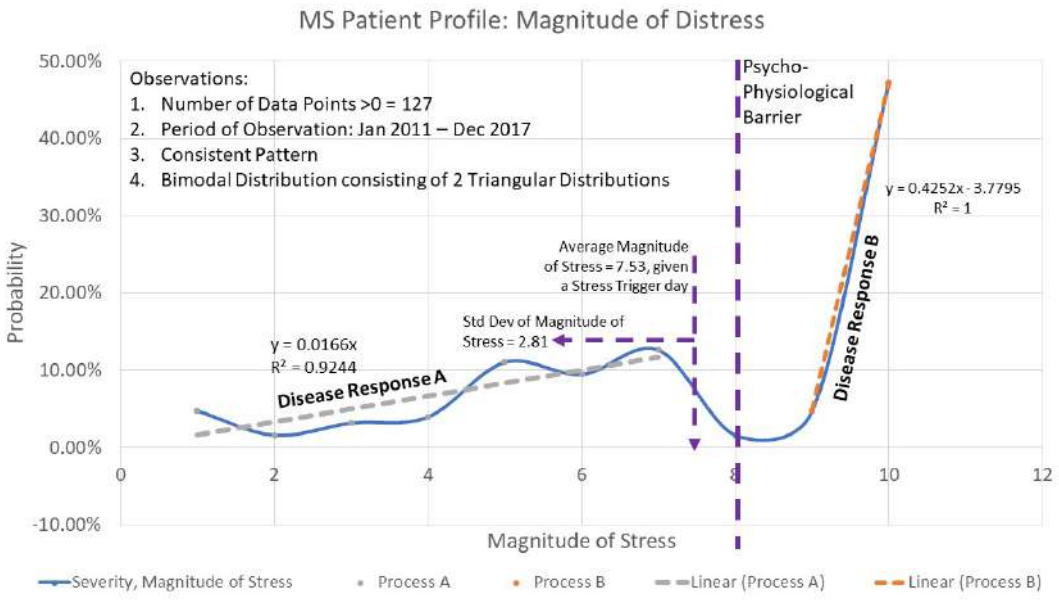

Figure 4: MS Patient's Stress Response Magnitude to Stress Triggers between Jan 2011 to Dec 2017.
Stress Response: The patient's reaction to stress triggers in terms of the magnitude of emotional distress experienced. Depicts two disease responses, A & B. Disease response B is what the patient experiences under extreme stress. Note that the transition between A & B is a dip and that the body's response appears to suppress severe responses.

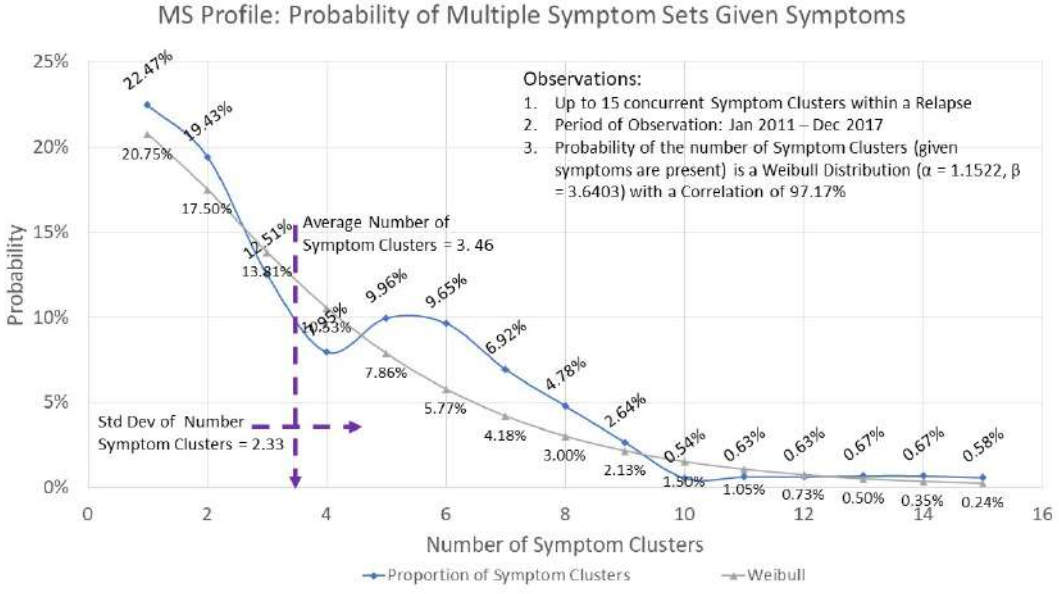

Figure 5: Probability of the number of Symptom Sets given Symptoms are present
Stress Response: The probability distribution of the number of symptom sets the patient experiences give the probability distribution of the arrival of stress triggers, Figures 2 & 3, and the patients distress experience, Figure 4.

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symptom sets are present, within the same relapse period, is defined by a Weibull Distribution with the shape & scale parameters α=1.1522 & β=3.6403, respectively. That is, few symptom sets are more likely than many symptom sets, and because α>1, the situation is worsening.

$$P(N_C|S_C) = \frac{\alpha}{\beta^\alpha} {N_C}^{\alpha-1} e^{-\left(\frac{N_C}{\beta}\right)^\alpha} \quad where\ \alpha = 1.1522, \beta = 3.6403 \qquad (6)$$

Remission Period: This is the Asymptomatic or Remission Duration (**Figure 6**) and is defined as the End Date of the last symptom set S_C of the previous Relapse Period, and the Start Date of the first symptom set of the subsequent Relapse Period. Otherwise, also known as the Remission Period. **Figure 6** shows the probability distribution of the duration of the asymptomatic remission periods between relapses. The Levy probability density function is the best fit and is of the form $\alpha {D_A}^\beta$ where D_A is the duration of remission or asymptomatic period with α=0.7474, β = -0.7918 and gives a correlation of 93.0% (the model and the data fit very well).

$$P(D_A) = \alpha {D_A}^\beta \Big|_{L=1}^{U=280} \quad where\ \alpha = 0.7474, \beta = -0.7918 \qquad (7)$$

This Levy Distribution shows that:

1. The average remission period is 38.3 days with a rare maximum of 280 days, given a Levy Distribution (**Figure 3**) of triggers with an average time between triggers of 8.7 days. A different probability distribution of triggers will result in different relapse & remission durations.
2. Short duration remission periods are more frequent (likely) than long duration remission periods.

Remission Rule: A general rule considers a remission period of 30 days intervening between two symptom sets as distinguishing separate relapses. Some consider this, an arbitrary [**54**] rule. In this study, the probability of a Remission Period (**Figure 6**) of at most 31.5 days is 66.67% or two-thirds of remission occurrences are less than 31.5 days. The average Remission Period is 38.3 days. The Hazari Data Set shows that remissions can be less than 3-days (**Figure 6**). Together our findings do not lend credence to the general rule. This 30-day definition would diagnose frequent short remissions followed by relapse as a continuous relapse and therefore, a progressive disease.

If a general rule is required, it is proposed that a remission is confirmed after 7 days (probability of 26.19%) of symptom free disease. With this new definition the diagnosis of progression would be reduced in 40.48% of the total MS cases.

Symptom Set Duration:

Figure 4 shows that there are 2 active distress magnitude Disease Responses, A & B. **Figure 7** shows that, because of these two Disease Responses, A & B, a bimodal distribution of Relapse Periods is observed. This bimodal distribution can be deconstructed for (i) Disease Response A, with probability $P(D_A)$ of a relapse duration D_A. This is a Weibull Distribution (α= 1.9425, β=13.6168) & (ii) Disease Response B, with probability $P(D_B)$ of a relapse duration D_B. This is a Normal Distribution (μ = 40.3983, σ=4.3506), and confirms that with MS there are distress mechanisms at play.

$$P(D_A) = \frac{\alpha}{\beta^\alpha} {D_A}^{\alpha-1} e^{-\left(\frac{D_A}{\beta}\right)^\alpha} \quad where\ \alpha = 1.9425, \beta = 13.6168 \qquad (8)$$

$$P(D_B) = \frac{1}{\sqrt{2\pi\sigma}} e^{\frac{(D_B-\mu)^2}{2\sigma^2}} \quad where\ \mu = 40.3983, \sigma = 4.3506 \qquad (9)$$

Since Disease Response B is a Normal distribution, this would imply that it is a more complex statistical process than Disease Response A, as it is the sum of multiple other processes. Disease Response A matches the MS survey results [**55**].

Duration Change Distributions: The rate of recovery (healing) is different from the rate of relapse. Deconstructing the change in the duration of symptom sets S_C into probability distributions, **Figure 8** shows that there are 3 probability distributions, $P(\delta_D|R1)$, P(R2) & $P(\delta_D|R3)$ with respect to increasing (relapse) and decreasing (recovery or remission) durations. That is, the underlying disease processes are different when either distress, triggers symptom sets or when the absence of distress, leads to remission.

Recovery Distribution R1 (left side of **Figure 8**) is indicative of an active process in the absence of Distress Triggers. This decreasing change δ_D in symptom sets duration is a Levy Distribution (α = 3.2780, β = 1.2441, H-Displacement = 1.2360 days) with a correlation of 93.1%. The H-Displacement is the horizontal offset required to fit the distribution to the data.

$$P(\delta_D|R1) = \alpha(\delta_D + H)^\beta \Big|_{L=2}^{U=47} \quad where\ \alpha = 3.2780, \beta = 1.2441, H = 1.2360 \qquad (10)$$

This Levy Distribution shows that:

1. In recovery, the subsequent symptom set duration tends to be similar rather than dissimilar.
2. Longer recovery occurs when symptom sets have long durations and quicker recovery when symptom set have short durations.
3. Sudden recovery (change in duration from long durations to short durations) is unlikely.

Relapse Distribution R2 (bottom right side of **Figure 8** shaded in green) is indicative of an active disease process and provides the vertical offset to Relapse Distribution R3 but not to the Recovery Distribution R1. R2 is a uniform distribution at the level of 2.8332%.

$$P(R2) = 2.8332\% \qquad (11)$$

This Uniform Distribution (**Figure 8**) shows that, under distress, the active statistical process is:

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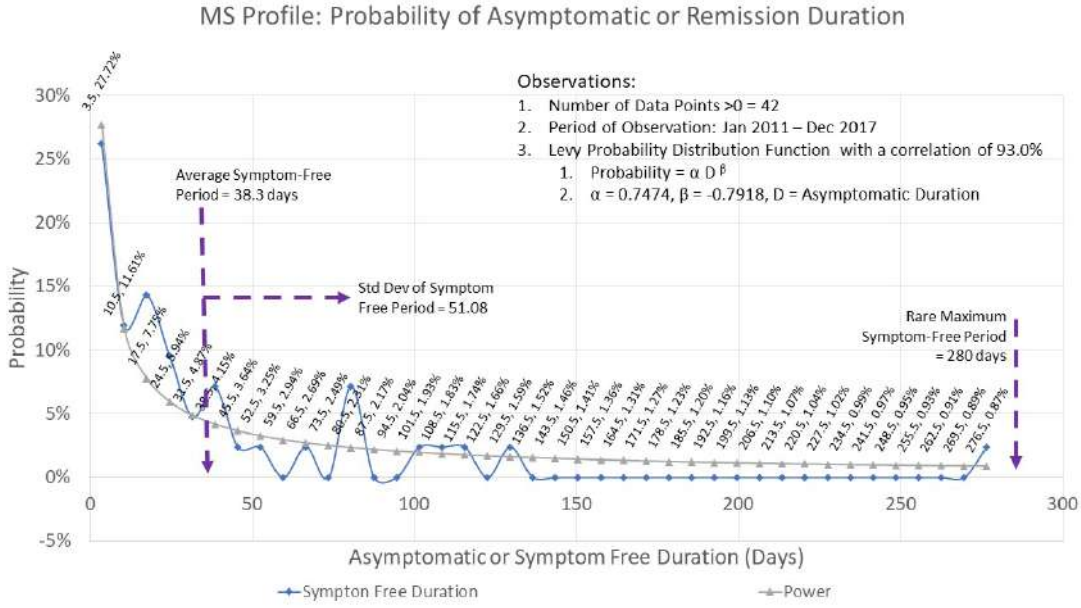

Figure 6: Probability of Remission Period or Asymptomatic Duration
Stress Response: The probability distribution of the remission duration the patient experiences give the probability distribution of the arrival of stress triggers, Figures 2 & 3, and the patients distress experience, Figure 4

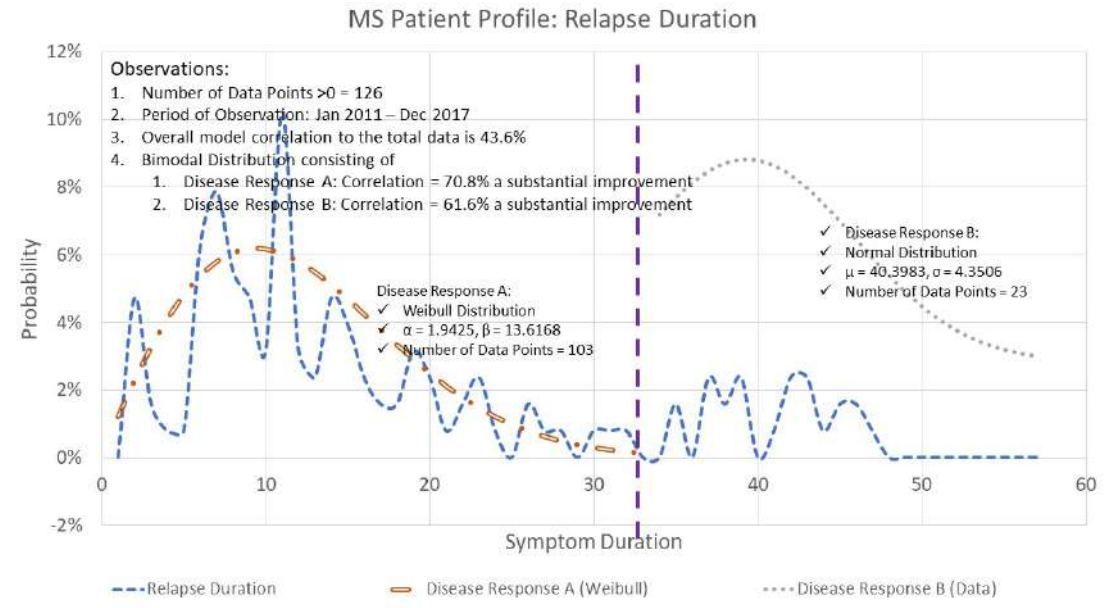

Figure 7: Bimodal Probability of Relapse Period
Stress Response: The probability distribution of the relapse duration the patient experiences give the probability distribution of the arrival of stress triggers, Figures 2 & 3, and the patients distress experience, Figure 4. It is a bimodal distribution and is split into two Disease Responses A & B.

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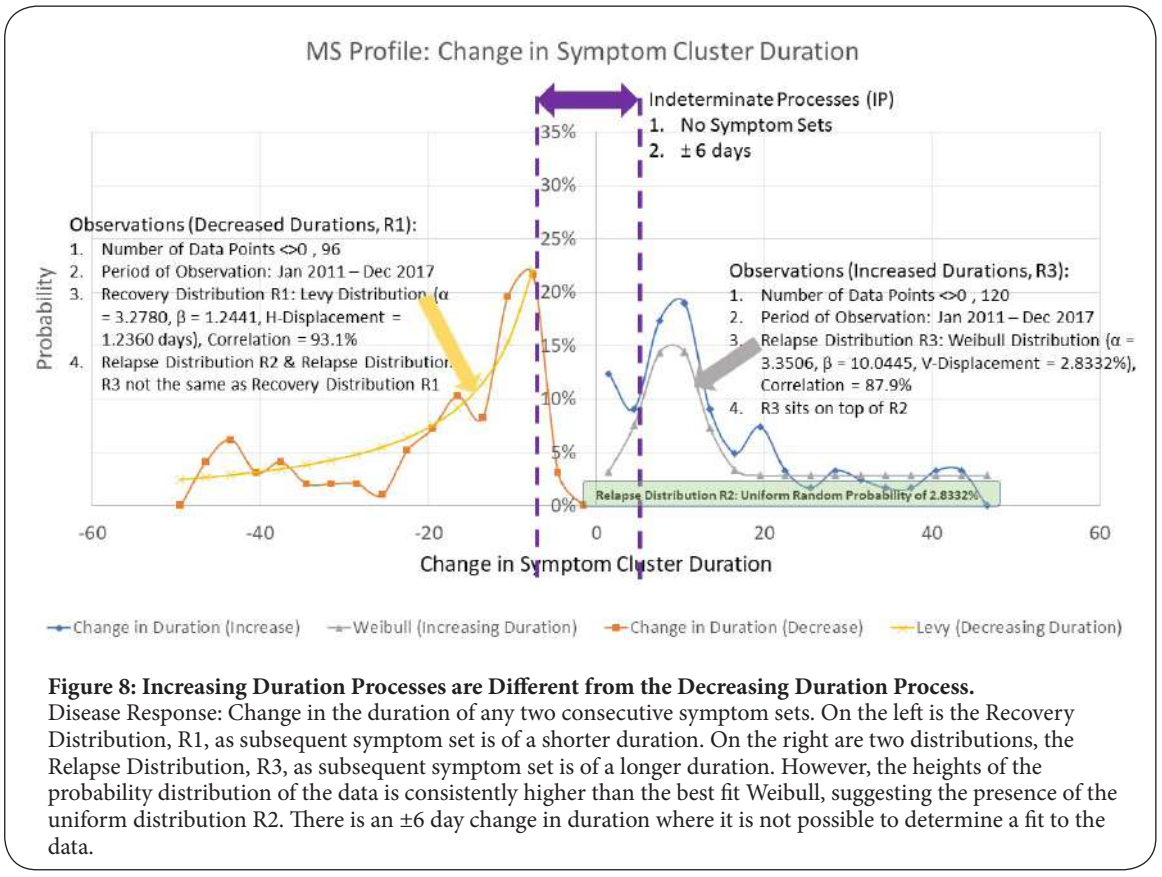

Figure 8: Increasing Duration Processes are Different from the Decreasing Duration Process.
Disease Response: Change in the duration of any two consecutive symptom sets. On the left is the Recovery Distribution, R1, as subsequent symptom set is of a shorter duration. On the right are two distributions, the Relapse Distribution, R3, as subsequent symptom set is of a longer duration. However, the heights of the probability distribution of the data is consistently higher than the best fit Weibull, suggesting the presence of the uniform distribution R2. There is an ±6 day change in duration where it is not possible to determine a fit to the data.

1. The only active underlying statistical process for any symptom set duration.
2. Adds to the probability of the debilitating processes.
3. Equally likely to produce short, medium, and long duration symptom set and produces the effect of randomness of symptom set durations.
4. The primary underlying background debilitating process could be the randomly distributed brain micro-lesions, but this requires clinical research to validate.

Relapse Distribution R3 is indicative of another active Disease Response in the presence of Distress Triggers less than 8. This is a Weibull Distribution (α = 3.3506, β = 10.0445, V-Displacement = 2.8332%) at a correlation of 87.9%. The V-Displacement is the vertical offset required to fit the distribution to the data.

$$P(\delta_D|R3) = V + \frac{\alpha}{\beta^{\alpha}}{\delta_D}^{\alpha-1}e^{-\left(\frac{\delta_D}{\beta}\right)^{\alpha}} \qquad (12)$$
$$where\ \alpha = 3.3506, \beta = 10.0445, V = 2.8332\%$$

This Weibull distribution shows that, under distress Relapse Distribution R3:

1. Is active in symptom set durations greater than 6 days.
2. Is a secondary process to that of Relapse Distribution R2.
3. Could imply temporary expansion of brain micro-lesions but this requires investigation.

Figure 8 & **Table 2** show that there exists an Indeterminate Response within the ±6 days where modeling of the Disease Responses is unclear. External to the region of Indeterminate Response, the shapes and parameters of these Disease Response distributions suggest that the underlying disease processes are different from each other.

Fundamental Disease Responses:

Figures 4, **7** & **8** provide 3 natural threshold conditions (i) Psycho-Physiological Threshold (ii) Asymptomatic Threshold & (iii) 33-Day Threshold. Together these thresholds divide the map, **Table 2**, into 3 regions:

1. The Null Response: **Table 2** shaded grey. This is the region where the Magnitude of Distress is insufficient to cause relapses of longer durations than those of Disease Response A.
2. Disease Response A: **Table 2** shaded green & blue. A Stress Response mechanism that triggers a Relapse Period of 33 days or less (33-Day Threshold) bounded by the Asymptomatic Threshold.
3. Disease Response B: **Table 2** shaded blue. A Stress Response mechanism that triggers a Relapse Period of greater than 33 days (33-Day Threshold) bounded by the Psycho-Physiological Threshold.

However, since Disease Response A has a low correlation

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(70.8%) and is bisected by the Psycho-Physiological Threshold, could Disease Response A be further deconstructed into more fundamental responses? The deconstruction produces 3 fundamental disease responses,

1. Disease Response A1: The shaded green triangle, bounded by Asymptomatic Threshold, the Psycho-Physiological Threshold, and the Indeterminate Response on the left. The probability $P(D_{A1})$ of symptom duration D_{A1} for the A1 response is a Levy Distribution ($\alpha = 57.9121, \beta = 2.5434$) with a much-improved model-data correlation of 95.7% (**Table 2**).

$$P(D_{A1}) = \alpha(D_{A1})^{\beta}\,|_{L=7}^{U=23} \;\; where\; \alpha = 57.9121, \beta = 2.5434 \quad (13)$$

2. Disease Response A2: Bounded by edge of the brown rectangle, shaded in blue, the Psycho-Physiological Threshold and 33-Day Threshold. The probability $P(D_{A2})$ of symptom duration D_{A2} for the A2 response is a Levy Distribution ($\alpha = 20.4686, \beta = 1.7315$) with a much-improved model-data correlation of 92.5% (**Table 2**).

$$P(D_{A2}) = \alpha(D_{A2})^{\beta}\,|_{L=10}^{U=32} \;\; where\; \alpha = 20.4686, \beta = 1.7315 \quad (14)$$

3. Indeterminate Response: Within the red rectangle, as the range of data is too great to provide a good fit to any probability distribution, even when modeling fundamental Disease Responses A1 & A2 with this data. This region (duration $D_{IR} \leq$ 6 days) concurs with the Indeterminate Response of **Figure 8**.

Figure 9 remaps the probability distributions of Disease Responses A1, A2 & B. They are different and distinct as (i) they have different scaling constants α, (ii) that the mode of Disease Response A2 is shifted to the right of that of Disease Response A1 and (iii) Disease Response A2 has a (right skewed) tail that is substantially fatter than that of Disease Response A1 because A2 sits on top of the Relapse Distribution R2. That is, the Relapse Distribution R2 covers the blue shaded area of **Table 2** when the Stress Magnitude is 9 or 10.

This analysis confirms that distress is a major factor in inducing MS symptoms. Comparing **Figures 4**, **6**, **7**, & **9** one can infer that there are 5 underlying pathologies of the disease states, Disease Response A1, A2, B, the Null Response (NR) and the Indeterminate Response (IR) which are observed as relapse and remission. These have quite different underlying statistical processes as evidenced by the shape of their response probability distributions and observed natural threshold conditions. This begs the question what causes this switching between these states? The answer to this is beyond the scope of this paper.

Duration Threshold:

Figure 10 shows how the disease stability and symptom set duration govern subsequent symptom set durations:

1. Indeterminate Response: The Indeterminate Response (symptom set durations <= 6 days) of **Table 2** corroborates the Indeterminate Response of **Figure 8** & **9**.
2. NT Response: This No-Triggers (NT) Response where there is sufficient recovery such that no symptom sets are present or subsequent symptom set duration is zero i.e., on recovery all disease responses (A1, A2, B & IR) revert to the NT Response. The NT Response obeys the R1 Probability Distribution of **Figure 8**.
3. Duration Threshold: For a given symptom set duration, the next duration cannot exceed the duration of the preceding symptom set, provided that the disease response is stable. This is equivalent to the Asymptomatic Threshold of **Table 2**. This is an upper bound.
4. Disease Stability: Illustrated by the curvy bidirectional red arrows **Figure 10** shows that the disease responses are not static as the Duration Threshold (blue line in **Figure 10**) prevents a change in duration that is greater than the current symptom set duration. Therefore, to produce a subsequent symptom set duration that is

   i. Less: requires a shift in the disease response to the left of the graph.

   ii. More: requires a shift in the disease response to the right of the graph.

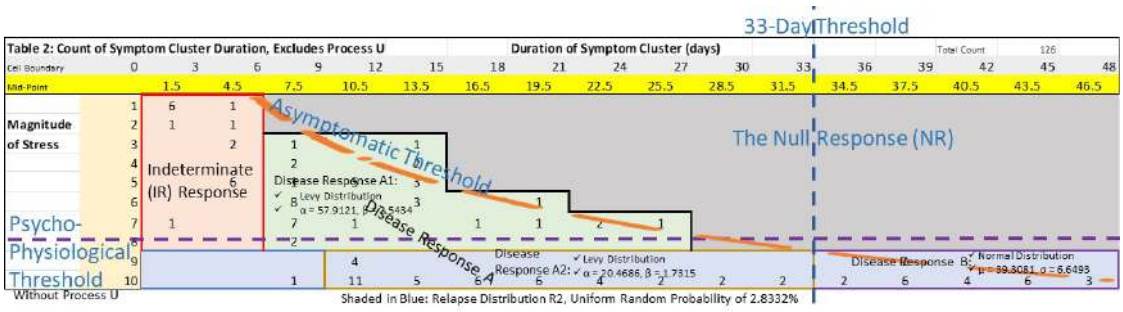
   iii. Changes in disease response is ongoing and the disease can switch between any disease response type A1, A2, B, IR & NT.

   Thereby, confirms dynamic stability.

5. Mapping Distributions: **Figure 11** shows how the probability distributions A1, A2, B, R1, R2, R3 are mapped back to their originating disease responses. Therefore,

   i. A1, A2 & B map to their respective probability distribu-

Table 2: Magnitude of Stress versus Duration of Relapse.



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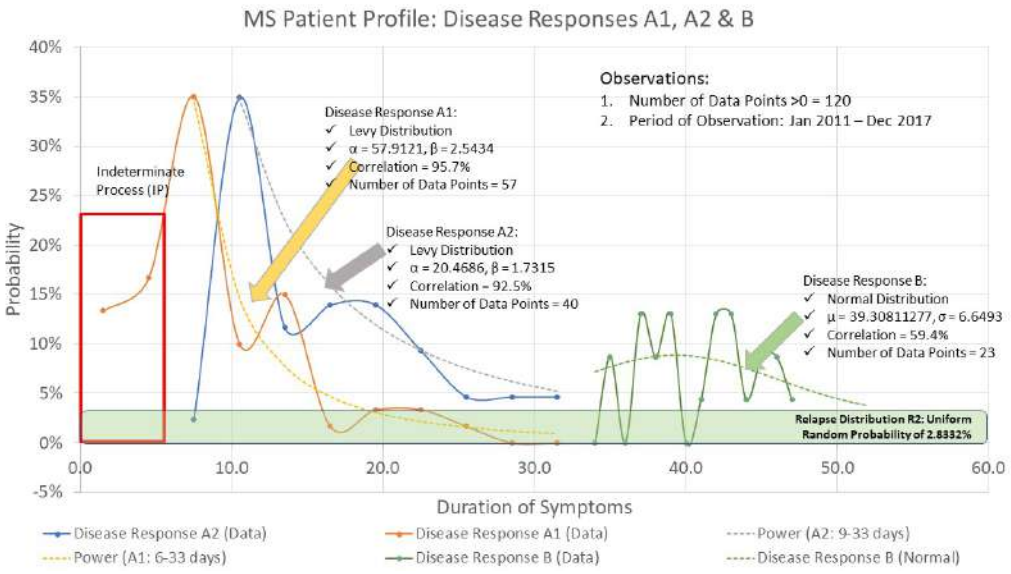

Figure 9: Fundamental Processes A1 & A2 Deconstructed from Process A.
Disease Response: Further examination of the data shows that Disease Response A can be split into 2 different responses A1 & A2. These are both Levy Distributions with A2 shifted to the right of A1. The data points that that would have altered the shape of these distributions are in the Indeterminate Process and Relapse Distribution R2. Therefore, the Levy Distributions hold. Note the substantial increase in the correlations with the data by splitting A into A1 & A2.

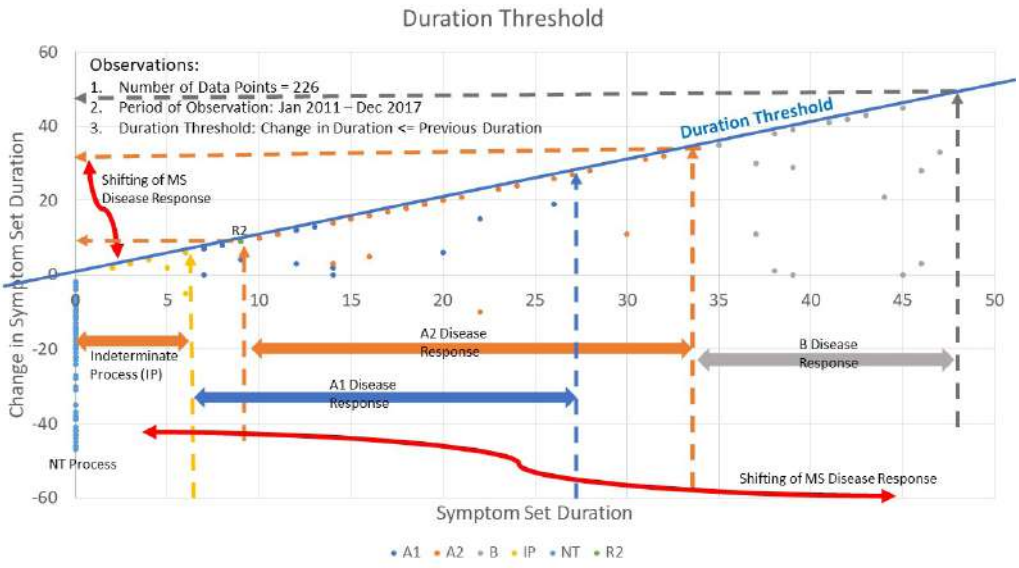

Figure 10: Duration Threshold Exposes Process Variability
Disease Response: Plotting subsequent symptom set duration versus the change in the symptom set duration shows two activities. The lower half of the graph show that remission occurrence is independent of previous symptom set duration. The upper half of the graph shows that a subsequent symptom set duration, as determined by the change in duration, can be at most, as long as the previous symptom set and upper bounded by the Duration Threshold. However, this is not observed in the same data. That means that the Disease Responses is shifting left or right, and underlying disease processes are dynamic.

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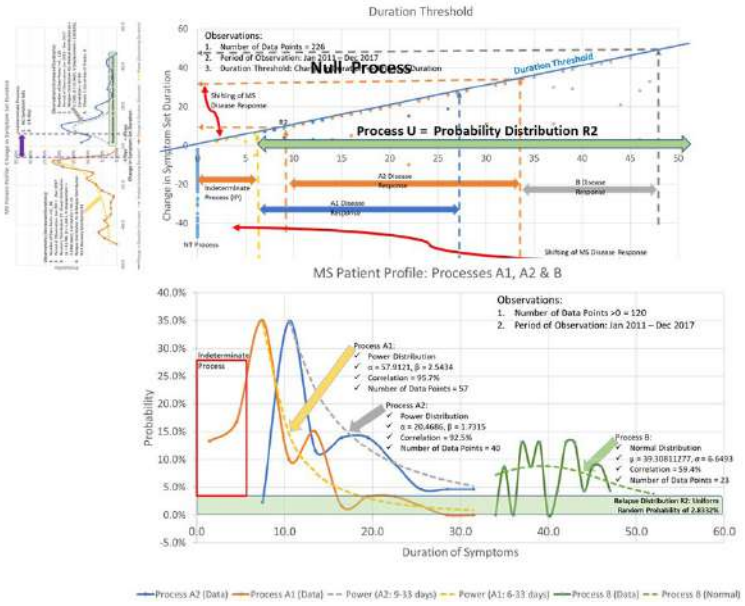

Figure 11: Mapping Probability Distributions A1, A2, B, R1, R2, R3 to the Respective Processes.
Disease Response: Combining Figures 8, 9 & 10 shows how the probability distributions of Disease Response A1, A2 & B map through the Duration Threshold to probability distributions R2 & R3. That is evidence that these underlying dynamic disease processes are quite sophisticated.

tions A1, A2 & B.
ii. The probability distribution R1, maps to the recovery response NT.
iii. The uniform distribution R2, maps to response U, the disease response below the Duration Threshold.
iv. R3 is the probability distribution of Relapse with R2.
v. The Null Response maps to the region above the Duration Threshold.

Note, that one observes that the MS disease probability distributions are right skewed. The exception is the recovery distribution R1. Compare for example, with the infectious disease COVID-19 [31,56] where the infectability and recovery probability distributions are left skewed, but the mortality distribution is right skewed (**Figure 12**). These two diseases provide further inferences that dynamic stability via regeneration and degeneration processes exists. A second inference, which needs further testing, is that disease probability distributions are right skewed when regeneration is failing and unable to overcome degeneration and left skewed when regeneration overcomes degeneration.

Findings: Mathematical Model of Symptom Sets

As reported earlier, from the 2,561-day period studied, 1,640 (64%) days were symptom free and the remaining 921 (36%) days were not. Distress-triggers (0-10) were recorded on 139 of these days causing 129 distress of magnitude 1-10. These produced 129 symptom sets or 2,239 relapse-symptom-days. A similar finding [9,42] that it is the number of stressors and not stressor severity or duration [43]. Duration is the inverse of frequency. The key to understanding symptom set onset and exacerbations is not the severity [43] of the Stressors but the severity of the resulting distress, the Stress Response, this concurs with other research [44,45] and could explain research findings that differ [14-17].

That is, given that the disease is present, every trigger caused a specific symptom set. The probability $P(N_C|S_C)$, equation (6), of the number of symptom sets is purely a function of the arrival pattern of the distress-triggers and not a function of the disease, itself. Likewise, remission period is purely a function of the absence of distress-triggers and not of the disease. It is proposed that distress-triggers exacerbate and expose the presence of the disease as 90% [54] of the disease is not observable, particularly in the early stages of MS.

Table 2 shows that the magnitude of distress S_E is a primary determinant of symptom duration and provides an easy method of determining the upper bound of the duration D_U of a symptom set that is independent of the operating characteristics of the distress trigger process. Given the magnitude of the distress S_E to the distress trigger, the Asymptomatic Threshold, using regression, is found to be a 2-parameter, single variable model of S_E,

$$D_U = \alpha e^{\beta S_E} \pm 1.5 \; days \; where \; \alpha = 3.9232, \beta = 0.2595 \quad (15)$$
$$R^2 = 93.63\%$$

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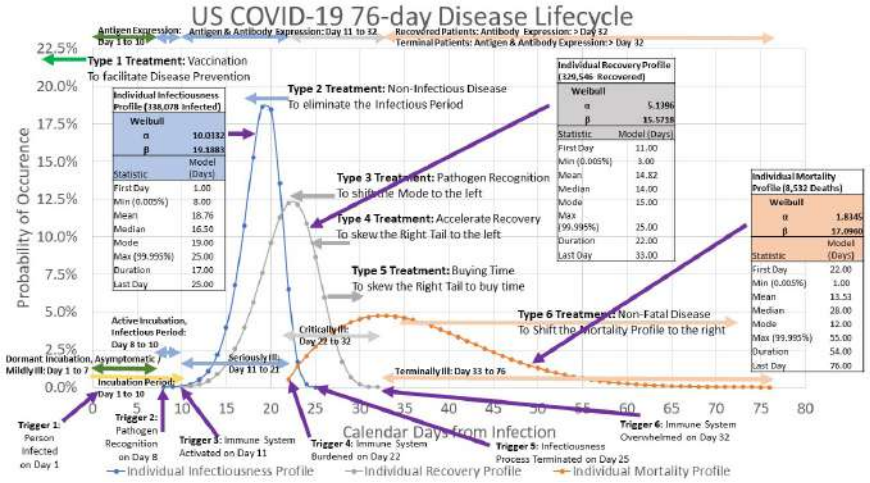

Figure 12: The 5-Stages of the US COVID-19 Infected Person's Response
Disease Response: These probability distributions were determined from the first 45-days of COVIC-19 pandemic counts. The figures the events that trigger the body's response to this variant. Most importantly patients' mortality starts at day 22 and subsequently become terminally ill by day 33. This analysis suggest that different opinions and strategies operate at different points in the disease.

And effectively a single parameter α model as a function of S_E,

$$D_U = \alpha e^{\frac{S_E}{\alpha}} \pm \gamma \; days \; where \; \alpha = 4, \gamma = 1.5 \quad (16)$$
$$R^2 = 93.74\%$$

With this patient data, the range of upper bound duration D_U is given by ±1.5 and parametrized as γ. This is to account for different patients having different ranges. For example, a magnitude 3 distress will have a symptom set duration upper bound D_U of 15 days if using the discrete data of **Table 2**. The smoothed function (16) provides 8.5 ±1.5 days or 7 to 10 days.

Conversely, (16) could be used to calibrate a patient's distress magnitude. Given the duration of symptom set, say 31 days, (16) would return a distress magnitude of 8. However, if the patient said that his/her distress magnitude S_E was 6, this patient would be 2 points or S_P below the Hazari Data Set reference and (16), in terms of this patient's S_E would be rewritten as,

$$D_U = \alpha e^{\frac{S_E + S_P}{\alpha}} \pm \gamma \; days \; where \; \alpha = 4, \gamma = 1.5, S_P = 2 \quad (17)$$

Once, this calibration is complete, it is possible to (i) determine which disease response is present, and (ii) compare patient data across many different patients. If the patient had a symptom set duration of between 18 & 21 days (**Table 2**), and the magnitude of distress triggered was 7, the underlying disease response is A1. Of course, if the duration was less than 6 days, this would signify an Indeterminate Response (IR) which appears to be a uniform distribution and more data is required to research this further. The lower bound of the symptom set duration D_L is 7 days for A1, A2 and B disease responses. Thus, mapping the data by distress magnitude S_E and duration of symptom set shows that for

1. Disease Response A1: This relationship suggests additional factors at play and that 90% of the symptom durations D_{A1} are within 7 and 15 days with all S_E are within 3 and 7.
2. Disease Response A2: Distress magnitude S_E is 10, 89.5% of the time, and 9, 10.5% of the time. Therefore, the duration D_{A2} of A2 symptom sets are given by equation (14) per **Figure 9**.
3. Disease Response B: Like Disease Response A2, Disease Response B has distress magnitude S_E of 10 only. Therefore, the duration D_B of B symptom sets are given by equation (9) in **Figure 9**.

Therefore, from a clinical perspective, only Disease Response A1, A2 and B are directly observable, and the MS symptom sets obey equations (13), (14) & (9), respectively, while being upper bounded by (17). Therefore, it is now possible to estimate symptom set durations.

Equation (17) can be used for cases where patients exhibit MS symptom sets with no apparent distress triggers. In these cases, S_P would have a high value, say 9, and any Stress Response less than 1, would trigger severe symptoms.

Since, a relapse consists of one or more symptom sets, the upper bound of a relapse duration $D_{U,R}$ would be the maximum of all symptom sets i to n, with duration upper bound $D_{U,i}$ plus the time t_i between relapse start and start of this symptom set, i.e

$$D_{U,R} = \max\{(t_i + D_{U,i}), .., (t_n + D_{U,n})\} \quad (18)$$

Where t_i is determined by the i^{th} trigger event, with the Haz-

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ari Data Set, $t_i - t_{i-1}$ is determined by equation (4), and $D_{U,i}$ is determined by equation (17). However, as a symptom within a symptom set may have reduced but not ended, there is a residual symptom. This is due to the permanent damage ρ within the central nervous system.

However, earlier research [45] suggests that the Kaplan-Meier survival curves of the probability of not reaching (i) Secondary Progression, (ii) Expanded Disability Status Scale (EDSS) score 3.0 and (iii) EDSS 6.0, are essentially straight lines of deterioration between year 6 and 36 of the MS disease process. **Table 3** evaluates the annual probability of reaching each of the three stages. It is increased by 2.5%, 2.3% and 1.8%, respectively, every year and decreases with increased disease severity. If one assumes that this a direct result of central nervous system deterioration, the annual change in the central nervous system damage δρ is 2.5%, 2.3% and 1.8%, respectively. This δρ decrease with severity, could be due to there being less healthy brain cells to damage.

That is, even though the disease responses and processes may be non-linear, the net effect on central nervous system deterioration is linear. This is an important consideration when mathematically modeling MS. However, this linearity issue may be in the measuring tool or ruler, EDDS. If EDDS is a non-linear tool then the results will appear to be linear with respect to that tool, but non-linear with respect to some other alternative measuring tool. That is, it should be important to understand the properties of the ruler.

The findings of this study can be summarized into four categories, (A) Disease Symptoms, (B) Disease Structure, and (C) Disease Dynamics (D) Alternative Interpretations, as follows,

Discussion: Disease Symptoms

1. MS symptom sets are Disease Symptoms [23] that are the Disease Responses to underlying Stressors. These Diseases Responses have statistical properties as presented in this paper for the Hazari Data Set. However, it is not within the scope of this study to determine the disease processes that cause these specific disease responses.
2. The onset and exacerbations of these Disease Symptoms is caused by the patient's distress or negative-emotional-stress-response, that are intrinsic to the patient's sensitivity, susceptibility, and condition.
3. A patient's distress is in turn triggered by Stressors. These Stressors maybe internal or external (as with the Hazari Data Set) to the patient and does not preclude both internal and external stressors being concurrently present.
4. Eliminating patient distress enables remission, and facilitating Stressors leads to relapse within 3 days.
5. Clinically, it may be argued that MS appears to be an unpredictable disease [6] because the emergence of symptom sets and their statistical properties, are dictated by the statistical properties of the Stressors. Different Stressors will have different statistical properties, and thus the appearance of unpredictably, across patients.
6. The statistical and mathematical basis for determining symptom set duration and the upper bounds of symptom set and relapse durations is provided. The mathematical model has parameters which may provide for variations in the patient's sensitivity, susceptibility, and condition with disease burden.
7. Research [46,47] has demonstrated that stress exposure can increase the likelihood of the disease emerging, as well as exacerbating preexisting conditions. That is, Stressors exacerbate and expose the presence of the disease, exhibited as MS symptom sets.

Discussion: Disease Structure

In terms of the Stress-Disease Meta Model this section relates to Effectors and Injury. Given that chronic demyelination significantly accelerates axonal loss [48], the current focus on autoimmunity as the cause of MS is based on correlation studies [49] and analogs or the resemblance [50,51] or mimicking human-animal histology. Whether inflammatory lesions, (the apoptosis of oligodendrocytes and neurons [52]), are the initial event in tissue injury is, however, currently uncertain [49], and the contribution of this cell death process to disease pathogenesis remains to be determined [52].

Given that this paper has shown that Stressors exacerbate and expose the presence of the disease, exhibiting as MS symptom sets, one can now focus on the subclinical (90% [54] of the) disease characteristics. The question is, how does one relate the distress originated 7 disease responses (A1, A2, B, IR, NR, NT & U) to, for example, the four fundamentally [4,53] different patterns of demyelination. Additionally, research suggests that there are changes to brain tissues even before the four Patterns are evident. This is corroborated by research that (i) reveal [70] subtle focal changes in the normal-appearing white matter which later develop into new T2-lesions, (ii) that subtle changes [71] in axons may precede the formation of classical MS plaques, and (iii) changes [72] well in advance

Table 3: Estimated Kaplan Meier Survival Gradient Between year 6 and 36.

MS Type	Year, x1	Probability, y1	Year, x2	Probability, y2	Gradient
Secondary progression	6	95.0%	36	20.0%	-2.5%
EDSS 3.0	6	90.0%	36	20.0%	-2.3%
EDSS 6.0	6	95.0%	36	40.0%	-1.8%

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of blood–brain barrier breakdown. Thus, do some of the 7 disease responses originate at these early changes? These are questions that only further research can answer.

Discussion: Disease Dynamics

In terms of the Stress-Disease Meta Model this section relates to Disease Processes, Regeneration and Degeneration. The cause of MS is still inconclusive [27] and the focus on auto-immune [1] mechanism of disease and risk factors have led to treatments but not a cure. Therefore, one could speculate that these factors are secondary effects of a true cause of the disease. Many questions remain, for example.

What causes the death of oligodendrocytes. Some observations [73] indicate that T-cells may not necessarily be responsible for triggering myelin destruction in some MS lesions. Thus, the influx of new oligodendrocytes [4,53] could be the immune system attempting to replace the dead oligodendrocytes and their myelin sheaths, and with T-cells removing associated debris.

Could the biochemical representations of distress emotions [74] and their byproducts have neurotoxic effects? Much of the current emotions research is centered around brain mapping [75]. While distress biochemistry does not appear to behave like excitotoxins, excitotoxins is not a new concept as research [76-78] provides evidence of neurotoxicity of glutamate, kainite, domoate and fibrin [65].

Given that myelin is considered "living" and myelinization is an active process [79] involving oligodendrocytes, then could the products of distress-based biochemical representations of emotions be a candidate (i) for neurotoxic effects on oligodendrocytes? (ii) vacuolation of myelin [80] during the construction of the myelin sheath? These require research to validate or negate. Considerations of a distress-based biochemical representations of emotions would also suggest that for future research, measuring the magnitude of distress (Stress Response) will likely give more consistent results than measuring the magnitude of the Stress, itself.

With MS one could ask if there is an approach to extend or enhance the body's remission processes as opposed to treating the changed distribution [81] of white blood cells, the relapse condition, where the clinical relevance of these biomarkers [82] in the context of the development and progression of MS remains unclear. On the other hand [83] "The decision to take the immune response in a certain direction is not made by one signal alone, instead many different elements act synergistically, antagonistically and through positive feedback loops to activate a Th1, Th2, or Th17 immune response."

Thus, given the presence of the Relapse Distribution R2 at relapse but not an equivalent at recovery, it is proposed that the body maintains a dynamic (as opposed to static) stability of wellness or disease by the interplay of two or more generic processes. Dynamic stability occurs when multiple processes are active, and the net result is an equilibrium state but introducing a disturbance or a perturbation would not change the equilibrium state. Static stability occurs when processes are at equilibrium state but introducing a disturbance or a perturbation would change the equilibrium state.

For example, (i) regeneration or revitalization and (ii) degeneration or deterioration, aging, or debilitation. This would concur with macrophages/microglia implicated in both demyelination or degeneration and re-myelination or regeneration in MS lesions [84]. On the other hand, static stability implies a single process and a single approach per that process to disease management. One's medical perspective determines how one formulates treatment strategies. For example, the analysis of COVID-19 [31,56] shows that three probability distributions must be present and suggests six different treatment strategies (**Figure 12**).

With dynamic stability, recovery occurs when the regeneration rate is greater than the degeneration rate. Similarly, relapse occurs when the regeneration rate is significantly less than the degeneration rate. In early-stage MS, recovery is present but gradually failing as mean duration [55] of the first remission is 71.32 months and that of second remission is 58.07 months. Thus, the cycling (**Figure 10** &**11**) between remission and relapse is due to the shifting dynamic stability in the presence of distress.

This dynamic stability has implications for the formulation of medical research and clinical trial objectives. For example, with a static stability model, the destruction of myelin sheath is the overt cause of MS as the primary disease. With a dynamic stability model, degeneration or demyelination and regeneration or remyelination are occurring all the time. The intricacy of the regenerative process is unknown [85], but myelin regeneration is observed. Thus, one could propose that the detection of myelin in the spinal fluid is evidence, not of the degenerative process, but of the unknown regenerative process failing, and therefore, a cure for MS may be found when this regenerative process is known.

Similarly, correlation is not cause. The interpretation that the altered population distribution of immune cell types under static stability, necessary means that specific types of immune cells are the immediate and direct cause of myelin destruction. Departing from this conventional wisdom, under dynamic stability, this no longer holds. With dynamic stability the new population distribution of immune cell types is just a recognition of the body's attempt to address (i) the necessary cleanup of dead, not the attack of live, oligodendrocytes and its associated myelin sheath and (ii) the failing unknown regeneration process. This is a likely scenario with an emotion induced mechanism that causes oligodendrocytes death and myelin destruction. Thus, even though MS may be observed as an auto-immune disease, it may involve a more subtle mechanism. Of course, the dynamic stability hypothesis needs research to be either vindicate or disprove.

Discussion: Alternative Perspectives

The purpose of empirical observations is to build theories to

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solve problems. Therefore, when considering how to interpret observations, the simpler (not simple) explanation is preferred (William of Ockham [86]). By properly structuring the analysis and discussion using the Stress-Disease Meta Model, the problem, and the disease definition, have been deconstructed into simpler components, providing a mathematical model that can be applied to other patient data with success. The simpler explanation is that distress directly causes an MS relapse. How this distress translates into a psychoneuroimmunoendocrinological or other process is beyond the scope of this paper.

Mathematics had become so sophisticated that it could be used to prove anything (Morris Klein [87]). The body of mathematical theory pertaining to MS needs to provide insights and not just be theoretically robust. Robustness is a necessary but insufficient condition for a mathematical treatment of a problem. Of the five mathematical models [27-29,33,34] considered in this paper only the last [34] provided an insight into the disease. Thus, the intention of any analysis of an investigation, is not just to model the phenomenon but to model the phenomenon to determine insights. Agreed this is more difficult to do than it sounds. In our model, the key insight is that distress directly determines disease behavior predictably and according to a mathematical form.

The need for an alternative interpretation is ever present as science is by consensus and thus the need for empirical falsification or corroboration, as all knowledge is provisional, conjectural, hypothetical (Karl Popper [88]). We have approached MS from a statistical and mathematical direction incorporating new statistical methods. In statistical methods, testing for a probability distribution, for example. Frequently, many probability distributions will fit a data set and many statistical tests will provide excellent fits even if the tails do not fit correctly because there isn't sufficient data in the tails. The point is to find a distribution that "makes sense" and one should especially look at how the mode and the tails fit the data. This is best accomplished by testing for many different distributions (i.e., many different H_0) and by viewing the results graphically, as many tests do not handle probability distribution tails well and the reason why one of the authors invented Wilcoxon Regression [31].

We have also focused on the data and not on existing theories. Looking at data and pathology from different perspectives can reveal and integrate findings in unexpected ways. This paper has provided a perspective of a direct mechanism of distress causing occurrence of nerve damage.

Conclusion

The effect of psychological stress on immune system and disease and outcomes is well discussed in the literature, including public guidance. The research has increasingly established stress as a cause of MS onset and exacerbations, development of lesions on MRIs, and reduction of quality of life. Research has considered diverse sources of stress including life stressors, war, pregnancy, social conflict. Coping is an individualized factor, and illness perception is feedback that increases stress. Self-reported stress associated with exacerbations in multiple sclerosis are well discussed, indicating a correlation, but lacking sufficient detail to permit the strict statistical scrutiny performed in this paper. Researchers have proposed ways to improve the detail of data gathered on the pathology of MS, but the detail for deeply probative statistical analysis has been lacking. Many studies have resorted to reviews and meta-analysis to derive meaningful results for fueling research.

This paper has analyzed the very detailed medical records of one MS patient spanning 8 years and been able to establish a direct relationship between distress and MS relapse, and to derive an equation linking magnitude of distress to characteristics of an MS relapse, by using statistical and mathematical methods.

This paper provides an approach to analyzing complex diseases and the role of stress, by gathering or self-reporting detailed data and then isolating the underlying statistical responses. As a result, the meta-etiology Stress-Disease Meta Model is proposed. It is suggested that future clinical studies focus on the frequency of stressors, and the magnitude of the distress rather than the magnitude of the broad spectrum of stressors. The empirical clinical observations and physiological-histological evidence presented by other researchers point to dynamic stability of the wellness-disease responses. It is possible to "trap" a patient with relapsing-remitting MS in a 'continuing relapse' that has the appearance of progressive MS by inducing distress at a frequency that makes for the appearance of no remission.

With reference to distress, it has been shown that MS is not an unpredictable disease. By identifying Stressors as the source of Disease Symptoms, prognosis can be better managed with statistical models. MS symptom sets, and thus remissions and relapses, which all provide evidence of a subclinical underlying disease can be affected through distress management. It is established that distress management reduces markers of disease activity and improves outcomes. The integration of previously independent fields of medicine appears to be paramount in considering the mechanisms of distress in MS that result in nerve damage. It is hoped that the research findings of this paper will inspire further research on symptom management, disease understanding and a cure.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	BS	PB	DH	JM
Research concept and design	--	√	√	√
Collection and/or assembly of data	--	√	√	√
Data analysis and interpretation	√	--	--	--
Writing the article	√	--	--	--
Critical revision of the article	√	√	√	√
Final approval of article	√	√	√	√
Statistical analysis	√	--	--	--

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