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Dynamic Meta-Analysis as a Therapeutic Prediction Tool for Amyotrophic Lateral Sclerosis

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1. Introduction

In this chapter, we present a new method, dynamic meta-analysis, which allows the examination of the underlying system dynamics of ALS utilizing the wealth of existing published experimental and/or clinical literature. We perform a small-scale feasibility study of the G93A SOD1 mouse model to show that dynamic meta-analysis can also be utilized to predict treatment outcomes in a high-throughput manner.

1.1 Leveraging the wealth of data

In 2010 alone, 980 articles were specifically published on the fatal neurodegenerative disease Amyotrophic Lateral Sclerosis (ALS), and the cumulative total literature base for this single intractable pathology exceeds 10,300 articles, according to a PubMed search. One might think that with this wealth of information we would have ALS well in hand. Yet, there is no available, life-extending treatment despite the extensive and detailed information obtained by thousands of researchers at the cost of billions of dollars. ALS remains one of the most intractable neurological diseases; there is no apparent quick fix, no smoking gun, and no obvious answers—just mountains of intertwined experimental observations recorded across a host of individual publications. Furthermore, ALS has been remarkably resistant to reductionistic attempts to pinpoint the underlying problem. Potential contributing defects, mutations, and regulatory failures have been cited across a broad range of categories, including axonal transport (Bilsland, Sahai et al.), cellular chemistry (Hayward, Rodriguez et al. 2002), energetics (Shi, Gal et al.), excitotoxicity (Roy, Minotti et al. 1998), free radicals (Bogdanov, Ramos et al. 1998), genetic damage (Nagano, Murakami et al. 2002), inflammation (King, Dickson et al. 2009), necro-apoptosis (Vukosavic, Dubois-Dauphin et al. 1999), proteomics (Wood, Beaujeux et al. 2003), as well as systemic origin (Dobrowolny, Aucello et al. 2008). Yet experimental correction or "treatment" of any individually identified potential contributor has failed to translate into clinically significant and reproducible results (Peviani, Caron et al.).

1.2 Identifying and utilizing the system dynamics of ALS for combination therapy

Based on current evidence, ALS may exhibit system-level abnormalities that emerge from the complexities and interactions of their underlying mechanisms (Mitchell 2009; Rothstein

2009). Like an engineering control loop with many elements that ends up with an unstably high feedback gain, ALS may initiate from the combined effects of many small deviations that, in and of themselves, might be considered normal. To address multiple contributors and their interactions, a distributed intervention like combination therapy is necessary. Combination treatment strategies are typically based on the assumed presence of system-level synergistic interactions, which could amplify the desired treatment effects. Thus, before a combination treatment can even be developed, the system dynamics and potential synergistic interactions must first be revealed. That is, we cannot "treat", for example, a high-loop gain abnormality if we are not aware of its existence and have no means to measure it. A further limitation to combination treatment research is the combinatorial explosion of treatment possibilities (often hundreds to thousands) that must be experimentally explored—a daunting task that is neither financially nor temporally feasible. What is needed is a tool or method that can both identify and utilize ALS pathology dynamics to pre-screen treatment combinations in silico, such that treatment combinations predicted to have the highest efficacies could be experimentally assessed first, and thus greatly speed the time from ALS treatment discovery to potential clinical treatment success.

1.3 Dynamic meta-analysis as a means of experimental and clinical prediction

Here we examine the use of a novel and innovative form of meta-analysis, which we call *dynamic meta-analysis*, as a tool that enables the necessary examination of system-level ALS pathology dynamics as well as the prediction of ALS combination treatment outcomes. Traditional meta-analysis, which aggregates the results of multiple, heavily overlapping clinical/epidemiological studies into a larger virtual study from which relationships across a broader array of conditions can be examined and overall statistical power can be increased, has been successfully used to examine individual clinical treatments (Miller, Mitchell et al. 2007; Pastula, Moore et al. 2010).

Much can and has been honed from using traditonal meta-analysis to examine clinical trials. However, clinical trials lack the advantages of in vitro and in vivo experimental models where we can perform protocols and obtain mechanistic insight that is not possible in human studies alone. To examine the dynamics of ALS in order to develop successful ombination therapies, we really need to examine the individual interactions and regulation of multipe cellular- and system-level interactions, which are either too complex, too inaccessible, or inappropriate for human experimentation. The ALS literature, particularly through superoxide dismutase 1 mouse models (G93A, G85R, etc), identified several such interactions and their regulation. What is needed is a method by which we can integrate the individual studies, each of which study different aspects of ALS (axonal transport, excitotoxicity, apoptosis, etc.), into the quilt that is ALS. This indeed does sound like a task for meta-analysis.

However, traditional meta-analysis is not an option for examining experimental literature. The ALS experimental literature base is simultaneously much larger than any single collection of clinical trials, and much less overlapping than clinical protocols. Dynamic meta-analysis overcomes the constraints of traditional meta-analysis by allowing the implicit inclusion of system interactions and explicit inclusion of time, two key ingredients necessary to examine pathology dynamics and subsequent combination treatments. In short, dynamic meta-analysis provides a manageable means to integrate the experimental data published by thousands of researchers into a unified view from which new ALS treatments and treatment combinations can be explored.

While a major strength of dynamic meta-analysis is that it does provide an approach for aggregating and recapitulating experimental studies, its application is by no means limited to experimental studies. The same method can certainly be used to dynamically examine clinical stuides. The advantages of the implicit inclusion of interactions and explict inclusion of time still apply.

1.4 G93A SOD1 mouse model as a test bed for dynamic meta-analysis

In this chapter we perform a small dynamic meta-analysis feasibility study utilizing the G93A SOD1 ALS mouse model literature to illustrate the potential power of dynamic meta-analysis to reveal key system dynamics, identify treatment strategies, and predict combination treatment outcomes in ALS. This model, developed over 15 years ago, is still the primary experimental model used to investigate ALS mechanisms and treatments.

2. The dynamic meta-analysis method

In this section, we provide the foundation, overview, and detailed processes involved in dynamic meta-analysis. The methods are generalized, such that they could be applied to any experimental or clinical dataset. We use the G93A SOD1 model as our detailed example of the construction, implementation, and analysis required for dynamic meta-analysis in this section. However, we reserve the specific dynamic meta-analysis predictions for the G93A SOD1 mouse model for the 3. Results section.

2.1 Traditional meta-analysis as a foundation

Traditional meta-analysis leverages an a priori model of relationships to generate a system-wide phenomenological model of the system. What makes this approach effective is the statistical weight of all the measured data behind the regressed coefficients. However, its limitations are that it does not explicitly permit the inclusion of time or the implicit examination of metric interactions. The a priori model used in traditional meta-analysis is based on the idea that all systems can be locally approximated algebraically as first order (essentially $\Delta Y = B \cdot \Delta X$ where X and Y are metrics within the system and B is a regression constant of proportionality). The a priori model is typically illustrated in the form of the meta-regression equation:

$$Y = B_1 \cdot X_1 + B_2 \cdot X_2 + B_3 \cdot X_3 + B_4 \cdot X_4 \ldots \quad (1)$$

2.2 Mathematical basis of "dynamic" meta-analysis

The central novel premise behind dynamic meta-analysis is that relationships in biological systems are better conceptualized as a first order differential equation ($dY/dt = B \cdot X$). Such an a priori model utilizing rates of change treats system relationships much like chemical reactions. Clearly, for much of what constitutes a biological system a reaction metaphor is not just a good approximation, it is literally true. Thus, the meta-regression equation for dynamic meta-analysis becomes

$$dY_1/dt = B_1 \cdot X_1 + B_2 \cdot X_2 + B_3 \cdot X_3 + B_4 \cdot X_4 \ldots \quad (2)$$

where X's are various effectors within the system, Y is one (of many) affected metrics and B's are the interaction gain coefficients. With this meta-regression equation, the concept of

time is introduced explicitly. Therefore, dynamic meta-analysis can incorporate experimental data from differing time-points and predict effects over time. These traits make dynamic meta-analysis unique, even when compared to advanced meta-analysis methods such as network analysis (Trelle, Reichenbach et al. 2011). While network analysis does use comparative relationships, it does not include interactions or show how relationship ratios change over time. Thus, where traditional or even advanced meta-analysis produces a static set of linear relationships, dynamic meta-analysis produces a set of differential equations. This results in an innovative way to examine pathology dynamics as we can look at how metrics change and interact over time rather than being limited to how they correlate at a single point in time. Currently, the only other available technique capable of implictly including interactions and explicity including time is relational modeling (Mitchell, 2009; Mitchell and Lee, 2008). In fact, dynamic meta-analysis is, itself, one form of relational modeling. However, traditional relational models typically do not provide the desired statistical weight of dynamic meta-analysis since only one primary study is included per interaction.

2.3 Overview of the dynamic meta-analysis process

Dynamic meta-analysis is similar to traditional meta-analysis in that it utilizes literature searches, inclusion/exclusion critieria, and data aggregation techniques. A key difference in the dynamic meta-analysis process, however, is the study structure and data extraction. In the following sub-sections of the chapter we provide the details necessary to perform each step of dynamic meta-analysis: determining the study scope, performing literature searches and study inclusion/excusion, developing structure, extracting data, aggregating extracted data, implementing dynamic meta-analysis, and analyzing dynamic meta-analysis results.

2.4 Defining the study scope

Just as in traditional meta-analysis, defining the scope is an important step. There are several things to consider, including the outcome goals of the project, the measures and timepoints to be included, the statistical weight, and the desired timeline of the project. There is no methodological limit on the number of studies, measures, and timepoints that can be included in dynamic meta-analysis. Rather, the researcher must impose those limits. There is a balance between including enough studies to obtain statistically significant results and the amount of man-hours it takes to perform dynamic meta-analysis. The one drawback of meta-analysis is it is by no means a completely automated process. Rather, humans must be involved at each step, to search and more importantly extract the data from included studies.

To assist in balancing workload and the time it takes to get preliminary results from dynamic meta-analysis, we divide dynamic meta-analysis into two parts: a feasibility study and a full study. A full study, as the name implies, encompasses all of the primary articles that meet the inclusion criteria. In contrast, a feasibility study can potentially have the same number and breadth of outcome measures as the full study, but utilizes a lesser number of included primary studies for each metric (i.e. a lower "n"). That is, the statistical weight is decreased. The advantage of performing an initial feasibility study goes beyond simply obtaining preliminary results more quickly. The initial results of the feasibility study also provide insight and direction, which can be used to fine tune the targeting of the full study (e.g. determining if more or less measures are needed or if the scope of the study needs revised, etc.).

2.5 Literature searches, inclusion and exclusion criteria

Literature searches are performed in a semi-automated manner, similar to a systematic review (see Cochrane Review instructions for a full description of this method). Here, we utilize keyword searches in PubMed. Our strategy is not to be over-limiting in our resulting study selection. Rather, we limit the size of our dynamic meta-analysis by decreasing the study scope instead of using highly selective inclusion/exclusion criteria.

For the dynamic meta-analysis presented in this chapter, we perform two different literature searches, Phase I and Phase II. The first literature search (Phase I) is an all-encompassing literature search for primary research studies/articles. Phase I inclusion results in ~1,803 papers, while Phase I exclusion leaves a remainder of 1,144 papers. These 1,144 articles are the studies/data sets for dynamic meta-analysis. The second literature search (Phase II) is for ALS review articles. Phase II inclusion results in ~200 reviews, while Phase II exclusion reduces the number to 52. The review articles are utilized for the purposes of structure and aggregation (to be discussed in the following sub-sections).

Phase I Inclusion Criteria:

- All studies must be from peer-reviewed journals, which are indexed in the United States National Library of Medicine and National Institute of Health PubMed database.
- Amyotrophic Lateral Sclerosis" or "ALS" in title/abstract
- "G93A" or "transgenic mouse" in title/abstract
- Most Recent 15 years
- Primary research artciles

Phase I Exclusion Criteria:

- articles without verifiable controls for each experimental metric utilized
- articles without quantitative, statistically significant results
- studies not measured at two or more time points

Phase II Inclusion Criteria:

- all studies must be from peer-reviewed journals, which are indexed in the United States National Library of Medicine and National Institute of Health PubMed database.
- "Amytrophic Lateral Sclerosis" or "ALS" in title/abstract
- clinical or experimental review articles
- most recent 5 years

Phase II Exclusion Criteria:

- articles focused on human case studies
- articles focused on assessment metrics
- articles focused on ALS variants with dementia
- articles focused on disease management
- articles focused on non-mechanistic based therapies

2.6 Structure: Outcome measures, interactions, and categories

Similar to traditional meta-analysis, dynamic meta-analysis utilizes outcome measures (measures that are calculated or derived from the included studies) as a means of prediction. Unlike traditional meta-analysis, dynamic meta-analysis also includes *interactions* between the outcome measures. However, due to the larger scope of dynamic meta-analysis compared to traditional meta-analysis, it is helpful to combine individual experimental metrics or outcome metrics into aggregates we refer to as *categories*. The outcome measures, interactions, and their respective categories, together, make up the dynamic meta-analysis structure (Figure 1).

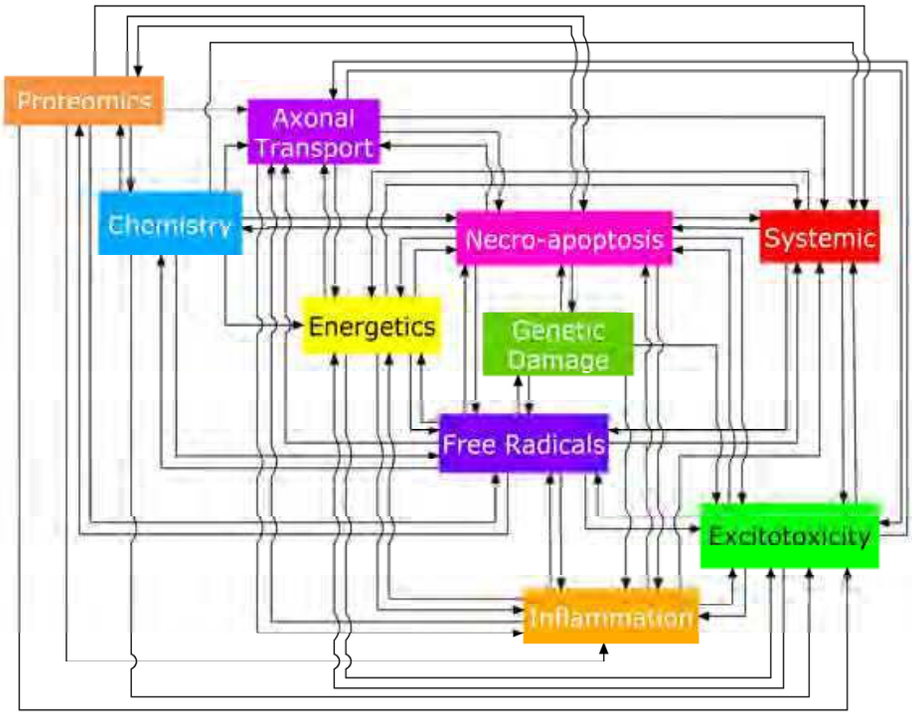

Fig. 1. Dynamic Meta-Analysis Feasibility Study Structure. Boxes represent the ten categories of outcome measures. Lines represent the 72 one-way interactions between categories of outcome measures. Systemics is shown in red as it represents the functional outcome metrics measured the in vivo G93A SOD1 mouse, and is used as the primary outcome for treatment evaluation (see Results). Categories are derived from the Phase II literature reviews. The outcome measures and their interactions are derived from the primary studies obtained from the Phase I literature search.

2.6.1 Category definitions

Aggregation of primary study metrics into categories balances the number and specificity of dynamic meta-analysis outcome measures with statistical weight. Too little aggregation will result in too disparate of a collection of very specific experimental mesasures or outcomes and will reduce the statistical weight of their predictions. In contrast, too much aggregation will result in outcome measures that are too broad; while this will increase their stasticial weight, it will also ultimately reduce the specificity of the dynamic meta-analysis predictions. Thus, the level, type, and implementation of aggregation will depend on the scope of the study, the number or primary studies utilized, as well as the desired statistical weight.

If the quantitative outcome metrics and their measured interactions come from the primary studies of Phase I, where do their categories come from? Categories are derived from the review articles of Phase II. Reviews do a nice job of providing key topics that are being researched by the field. For this feasibility study, reviews were analyzed for common research topics, based on broad categories of related physiological measures. For example, all measures of dynein, kinesin, mitochondrial transport, neurofilament transport, and neurofilament transport, etc, were grouped into the category outcome measure "Axonal Transport". Key terms were then extracted from these topics and used to sort the primary studies, and their respective outcome measures, into the following categories (definitions

follow at the end of this sub-section): axonal transport, chemistry, energetics, excitotoxicity, free radicals, genetics, inflammation, necro-apoptosis, proteomics, and systemics. Reviews were also used to preliminarily determine which categories are inter-related (without having to examine each and every primary article). This is extremely helpful for development of the feasibility study. The quantitative specifics of the data aggregation process are discussed in Data Aggregation, while the category definitions are given below.

Excitotoxicity: encompasses measures of electrophysiology; ion, neurotransmitter, and buffer concentrations; activation of ionotropic/metabotropic receptors (Ikonomidou, Qin Qin et al. 1996; Dunlop, Beal McIlvain et al. 2003; Van Damme, Leyssen et al. 2003); altered excitability related to sodium (Kuo, Schonewille et al. 2004; Kuo, Siddique et al. 2005); and transport and pump capacity (Guatteo, Carunchio et al. 2007), causing toxic over-activation.

Axonal transport: encompasses measures of the anterograde and retrograde transport of cargos, such as mitochondria, neurotransmitters, neurofilaments, and endosomes/ lysosomes, as well as the measures of the involved machinery, such as the molecular motors kinesin and dynein. The most recognized impairments and their measures include mutations to cargos (Meyer and Potter 1995; Wong, He et al. 2000) and molecular motor cargo carriers (Hafezparast, Ahmad-Annuar et al. 2003; Teuchert, Fischer et al. 2006; Mitchell and Lee, 2009) that prevent the cargo from be appropriately bound to either dynein or kinesin. Other deficits include correlations to energetics, such as decreased mitochondrial transport or a decrease in overall transport due to a drop in mitochondrial potential (Ackerley, Grierson et al. 2004).

Energetics: encompasses measures of all machinery and processes related to cellular respiration and production of cellular ATP (Echaniz-Laguna, Zoll et al. 2002). Energetic contributors include impairments to the cellular machinery responsible for the production of ATP, especially mitochondria (Kong and Xu 1998; Sumi, Nagano et al. 2006), whose dysfunction also leads to accumulation of free radicals and calcium. Overburdened energetic capabilities because of increased homeostatic and transport demands from excitotoxicity (Dupuis, Oudart et al. 2004) have also been observed.

Genetic damage: encompasses measures of an extremely diverse spectrum of either inherited or sporadic mutations resulting in cellular dysfunction (Tanaka, Niwa et al. 2006). The most widely known genetic mutation, accounting for 2% of all ALS cases, is superoxide dismutase-1 (SOD1), which has over 100 known different mutations (Banci, Bertini et al. 2008) (for list, see www.alsod.org) that result in a gain of one or more toxic properties that are independent of the levels of SOD1 activity (Stathopulos, Rumfeldt et al. 2003).

Proteomics: encompasses measures of protein folding, degradation, and translation, which become impaired, resulting in defective essential proteins, toxic accumulation of aggregates or aggresomes, and inhibition of organelle function (Watanabe, Dykes-Hoberg et al. 2001; Urushitani, Kurisu et al. 2002; Rumfeldt, Lepock et al. 2009).

Chemistry: encompasses measures of aberrant cellular chemistry, enzymatics, or catalysis (Tiwari, Xu et al. 2005; Tokuda, Ono et al. 2008) that results in oxidative damage and metal mishandling that can be seen alone or in conjunction with SOD1 mutations.

Inflammation: encompasses measures of immune-induced inflammation, including astrocyte (Nagai, Re et al. 2007) and microglia (Hall, Andrus et al. 1998) counts, gliosis and the release of nitric oxide and proinflammatory cytokines, which in combination with impaired growth factors/trophic support (Narai, Nagano et al. 2005; Kadoyama, Funakoshi et al. 2007), further inhibit the neural environment.

Free radicals: encompasses measures of oxidation or inflammation-induced nitric oxide, but particularly the accumulation of reactive oxygen species, such as the superoxides and peroxides that are associated with mitochondrial dysfunction or failure. Free radicals initiate reactions that damage DNA (Pehar, Vargas et al. 2007).
Necro-apoptosis: encompasses the measures of cell death, including the signaling cascades, their constituents, and machinery, which promote cell death. The final destination of an ALS affected motoneuron is cell death either through inflammation-induced necrosis or more likely through apoptosis (Mattson and Duan 1999) via the activation of stress response and caspase pathways (Beere 2004; Gifondorwa, Robinson et al. 2007).
Systemic: encompasses invivo measures of function in the G93A mouse model (Derave, Van Den Bosch et al. 2003). It includes measures of muscle weakness, atrophy, fasiculations, denervation and ultimately loss of function that decreases essential stimulatory retrograde signaling, causing further progression of the diseased state.

2.6.2 G93A feasibility study structure

The dynamic meta-analysis structure is best illustrated like an engineering process flow diagram. Here we show in Figure 1 the categories of outcome measures (boxes) and their interactions (lines). Based on the presented study structure, we determined that there are minimally 72 interactions between the 10 categories of outcome measures. Thus, the minimum number of primary studies to be included in the feasibility study is 72, one for each interaction. Note that we define a primary study as an experiment that measures the interaction between two outcome measures. Therefore, a single published primary experimental article can, and often does, contain more than one primary study. However, it is easier to think of each interaction as needing at least one primary article, and thus, approximately 72 primary articles are need for data extraction to complete a minimalistic feasibility study. The differences between the full and feasibility study structure are shown in Figure 2.
Even for a feasibility study, an "n" of one for each interaction may not sound like meta-analysis, but keep in mind that there are multiple interactions contributing to the effect and prediction of each category. For example, in the structure presented in Figure 1, there are 3-10 interactions for each category. Therefore, 3-10 primary studies contribute to the prediction of each category of outcome measures. That range is in line with the number of primary studies per outcome measure that we might expect for a traditional meta-analysis.

2.7 Extracting data

Quantifiable data is extracted from included primary study figures and tables. Figure 3 shows a hypothetical example of the type of data figure one typically seen in the G93A literature. The Y-axis is typically the affected measure (in this case, percent of cargos travelling retrogradely) and the X-axis is typically the controlled measure (glutamate concentration in our hypothetical example). Additionally, the measure is usually quantified in both the wild-type and G93A mice populations.
Upon extraction, data is normalized to make it unitless. That is, we only look at the relative changes between measures. In this example data, the wild-type retrograde transport went down by ~20% with a 40% increase in glutamate concentration, whereas the SOD1 retrograde transport went down by ~25% with a 40% increase in glutamate concentration.

Therefore, the slope or gain (dY/dX) for wild-type is -0.2 for the interaction from glutamate to retrograde transport. Correspondingly, the gain, for SOD1, is -0.25. Because we only calculate relative changes in dynamic meta-analysis, the magnitude of the gain utilized is actually the relative difference between the wild-type and SOD1 gain magnitudes, (|SOD1| – |wild-type|)/|wild-type|, or [(0.25) – (0.20)]/(0.25) = 0.25, and the sign of this final gain value for this example is net negative (-). Applying the gain of the experimental outcome measures to the category measures, the interaction *from* the category outcome measure of excitotoxicity *to* the category outcome measure of axonal transport is -0.25. Finally, we divide the gain by the time point (or in the case of a feasibility study, the *to* category time constant) to obtain the interaction coefficient (B) used in Equation 2.

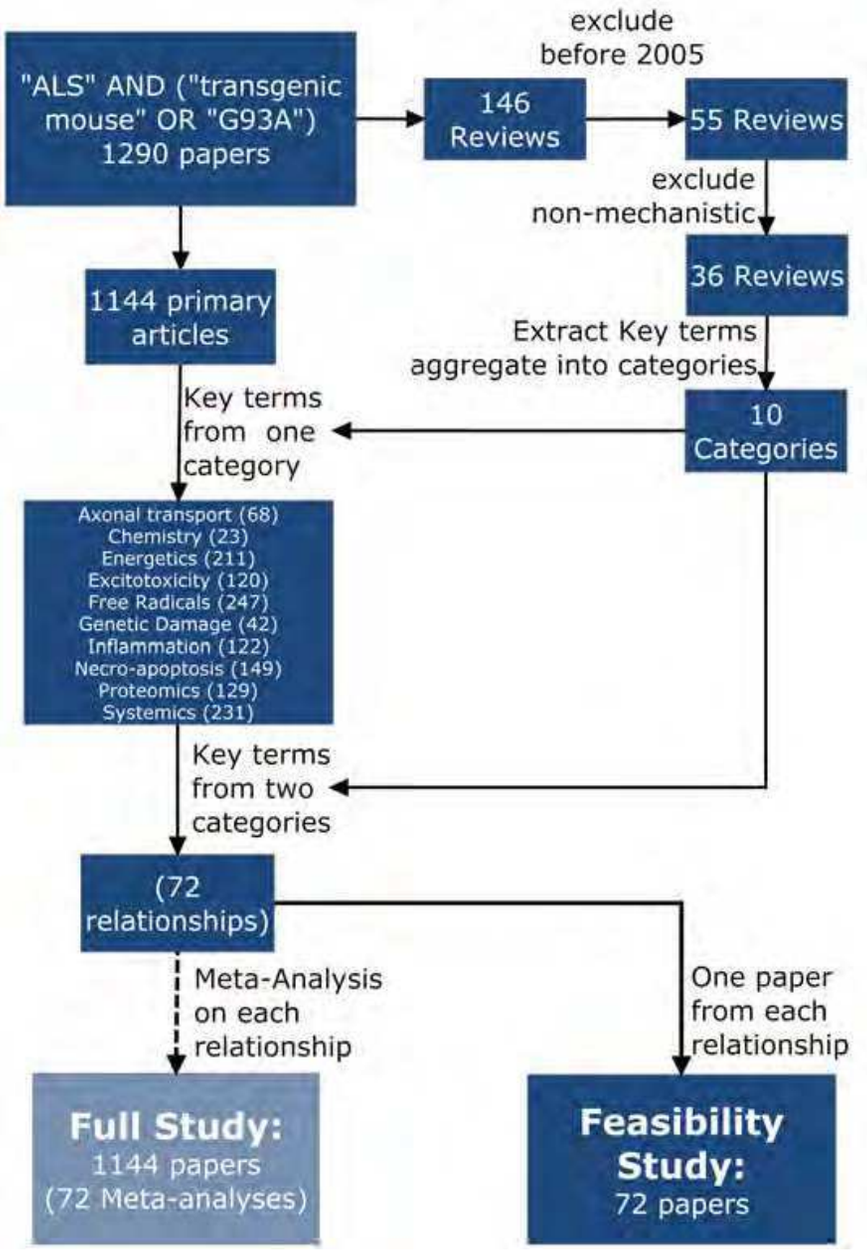

Fig. 2. Scope of dynamic meta-analysis study for the G93A SOD1 mouse model of ALS: feasibility study versus a full study.

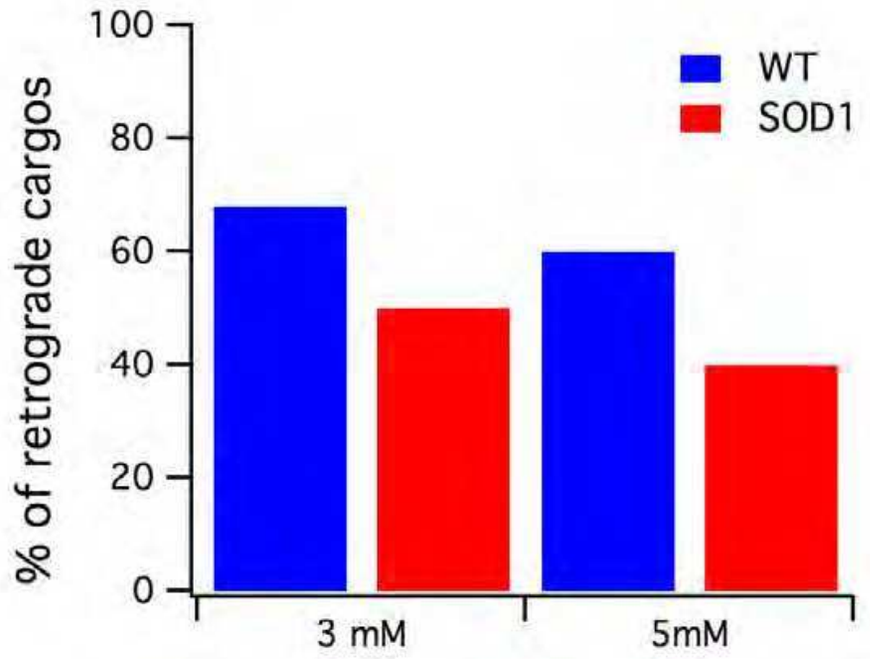

Fig. 3. Example data from a prototypical primary study.

2.8 Quantified data aggregation

For a category-level feasiblity study, such as presented here, it is appropriate to take a non-parametric approach to aggregating the quantitative experimental measures, as the aggregated relationships too disparate to make normalization practical. Consequently, gains were first qualitatively grouped into "small," "medium," or "large". Based on the overall range and resolution of the quantified category interaction magnitudes obtained from the primary studies, numerical gain values for small, medium, and large were set to 0.33, 1, and 3, respectively. However, other values were also explored (e.g. 0.5, 1, and 2; 0.25, 0.5, and 1 etc.) with no qualitative change in result. Table 1 lists the relative magnitude and sign of the category relationships and the primary references from which data was extracted.

Additionally, the corresponding time points for each category utilize a qualitative grouping of small, medium, and large. Based on our mathematical implementaiton of the time points, which is analagous to that used with time constants, we refer to the time points as time constants. Their numerical values and scaling are chosen based on the average onset of associated changes documented for a particular category using the G93A SOD1 mouse model time course. For example, measurable changes are occurring by day 40 in axonal transport, such as the appearance of aggregates and changes in cargo distribution (Kieran, Hafezparast et al. 2005; Teuchert, Fischer et al. 2006); thus, 40 days is used as the time constant for that category. Using the range and resolution of documented changes in G93A over all of the categories, the small, medium, and large time constants are set to 40, 80, and 120 days, respectively (Table 2).

From	To	Size	Sign	Primary Reference(s)
Axonal Transport	Axonal Transport	M	-	(Kieran, 2005; De Vos, 2007; Zhang, Strom 2007)
	Energetics	S	-	(Sakama, 2003; Miller , 2004; De Vos, 2007)
	Excitotoxicity	S	-	(Hiruma, 2003; Stevenson, 2009; Tateno, Kato, 1999)
	Necro-Apoptosis	M	+	(Collard, 1995; Ackerley, 2004)
	Inflammation	S	-	(Brooks,1991; Sasaki, 1996)
Chemistry	Systemic	M	+	(Tiwari, 2005; Ludolph, 2006; Watanabe, 2007; Hozumi, 2008)
	Axonal Transport	S	-	(LaMonte, 2002; Strom, 2008)
	Excitotoxicity	S	+	(Kawahara, 2004; Sasabe, 2007)
	Energetics	S	-	(Wendt, 2002; Lee, Shin, 2008)
	Free Radicals	S	+	(Poon, 2005; Furukawa, 2006)
	Necro-Apoptosis	M	+	(Elam, 2003; Kiaei, 2007; Lee, Shin, 2008)
	Proteomics	M	+	(Lindberg, 2002; Bergemalm, 2006; Rumfeldt, Stathopulos,2006)
Excitotoxicity	Axonal Transport	S	-	(Hiruma, 2003; Tateno, 2008; Stevenson, Yates. 2009)
	Excitotoxicity	M	+	(Rothstein, 1990; Rothstein, 1995; Kuo, 2004; Damiano, Starkov, 2006; Kuwabara, 2007)
	Energetics	L	-	(Beal, 1992; Nicholls, 1998; Jabaudon, 2000; Ellis, 2003)
	Free Radicals	L	+	(Kruman, 1999; Kruman, 1999; Carriedo, 2000; Ellis, 2003)
	Inflammation	L	+	(Hewett, 1994; Cholet, 2002; Barbeito, 2004)
	Necro-Apoptosis	L	+	(Liu, 1999; Sun, 2006; Gibb, 2007; Boutahar, 2008)
	Systemic	S	+	(Bittigau, 1997; Corona, 2007)
Energetics	Axonal Transport	M	+	(Sickles, 1990; Magrane, 2009)
	Excitotoxicity	L	+	(Beal, 1992; Agrawal, 1996; Ellis, 2003; Nicholls, 2003)
	Energetics	M	+	(Mattson, 1999; Mattiazzi, 2002)
	Free Radicals	L	+	(Mattson, 1999; Liu, 2002; Cassina, 2008)
	Inflammation	M	+	(Levine, 1999; Bilsland, 2008)
	Necro-Apoptosis	L	+	(Kruman, 1999; Kaal, 2000; Guegan, 2001; Dupuis, Gonzalez de Aguilar, 2004; Ilzecka, 2007; Knudson, 2008)
	Systemic	M	+	(Verstreken, 2005)
Free Radicals	Axonal Transport	S	-	(Chou, 1996; Chou, 1996; Ferrante, 1997)
	Chemistry	S	+	(Poon, 2005; Furukawa, 2006)
	Excitotoxicity	S	+	(Kruman,1999; Kruman, 1999; Ellis, 2003)
	Energetics	L	-	(Liu, 1996; Liu, 1999; Mattson, 1999; Liu, 2002; Cassina, 2005)
	Free Radicals	M	-	(Liu 1996; Liu. 1999; Cookson, 2002; Cassina, Pehar 2005; Pehar 2007)

From	To	Size	Sign	Primary Reference(s)
	Genetic Damage	M	+	(Aguirre, 2005; Mitsumoto, 2008)
	Inflammation	M	+	(Hensley, 2006; Liu, 2008; Nagai, 2007; Pehar, 2005)
	Necro-Apoptosis	L	+	(Chen, 2009; Estevez, 1999; Pehar, 2005; Pehar, 2007; Wood, 1995)
	Proteomics	S	+	(Dalle-Donne, 2007; Poon, 2005)
	Systemic	S	+	(Dalle-Donne, 2007; Poon, 2005; Kato, 2005; Mahoney, 2006; Mitsumoto, 2008; Sohmiya, 2005)
Genetic Damage	Excitotoxicity	M	+	(Kawahara, 2004; Ignacio, Moore, 2005; Kawahara, 2006)
	Free Radicals	S	+	(Armon, 2005; Wiedau-Pazos, 1996)
	Genetic Damage	M	-	(Armon, 2005; Jiang, 2005; Muller, 2008)
	Inflammation	S	-	(Puttaparthi, 2005; Di Giorgio, 2007; Puttaparthi, 2007)
	Necro-Apoptosis	M	+	(Locatelli, 2007; Lu, 2000)
Inflammation	Axonal Transport	S	-	(Chou, 1996; Kaasik, 2007; King, 2009; Morimoto, 2007)
	Excitotoxicity	M	+	(Hewett, 1994; Cholet, 2002; Pehar, 2004)
	Energetics	S	-	(Cassina, 2008; Cassina, 2005; Takeuchi, 2005; Bilsland, 2008)
	Free Radicals	L	+	(Hensley, 2006; Nagai, 2007; Pehar, 2007)
	Inflammation	M	-	(Gowing, 2008; Puttaparthi, 2005; Schiffer, 1996)
	Necro-Apoptosis	L	+	(Collard, 1995; Ackerley, 2004)
	Systemic	S	+	(Hall, 1998; Cassina, 2005; Cho, 1999)
Necro-Apoptosis	Axonal Transport	S	+	(Ackerley, 2004; Collard, 1995)
	Chemistry	S	-	(Kiaei, 2007; Elam, 2003; Lee, 2009)
	Excitotoxicity	L	+	(Gibb, 2007; Sun, 2002; Liu, 1999)
	Energetics	L	-	(Guegan, 2001; Guegan, 2002)
	Free Radicals	M	+	(Raoul, 2002; Raoul, 2005)
	Genetic Damage	S	+	(Muller, 2007; Raoul, 2006)
	Inflammation	L	+	(Hall, 1998; Cassina, 2005)
	Necro-Apoptosis	L	-	(Gonzalez de Aguilar, 2000; Gonzalez de Aguilar, 1999)
	Proteomics	M	+	(Gal, 2007; Gal, 2009; Yamashita, 2007)
	Systemic	M	+	(Li, 2007; Narai, 2005)
Proteomics	Axonal Transport	M	+	(Eaton, 2005; De Vos, 2007; Sasaki, 2005)
	Chemistry	M	+	(Rumfeldt, 2009; Atkin, 2006)
	Excitotoxicity	S	+	(Rothstein, 2005; Vanoni, 20040
	Free Radicals	S	+	(Aquilano, Rotilio et al. 2003; Clement, 2003)
	Inflammation	M	+	(Stieber, 2000)
	Necro-Apoptosis	M	+	(Urushitani, 2008; Atkin, 2008; Gal, 2007)

From	To	Size	Sign	Primary Reference(s)
	Proteomics	S	-	(Puttaparthi, 2007; Morimoto, 2007; Cheroni, 2009)
	Systemic	M	+	(Turner, 2005; Bucher, 2007)
Systemic	Excitotoxicity	S	+	(Kuner, 2005 ; Pieri, 2008)
	Energetics	S	-	(Wendt, 2002; Zhao, 2006)
	Free Radicals	S	+	(Mahoney, 2006; Pierce, 2008)
	Necro-Apoptosis	S	+	(Martin, 2000; Patel, 2010)
	Systemic	S	-	(Nagano, 2005; Deforges, 2009)

Table 1. Parametric gains for category interactions. Interactions are listed directionally-oriented *from* the category imposing the effected *to* the category being affected. The sign indicates whether the interaction is increasing or decreasing the category, and size (small, medium, large) qualitatively represents the gain magnitude (see Extracted Data Aggregation).

Category	Time Point (days)
Axonal Transport	40
Chemistry	40
Excitotoxicity	80
Energetics	80
Free Radicals	80
Genetic Damage	40
Inflammation	120
Necro-Apoptosis	120
Proteomics	40
Systemic	120

Table 2. Feasibility study time constants utilized for the calculation of the interaction term (B), as shown in Equation 2. Time points are aggregated from primary studies.

2.9 Implementation

Differential equations, in the form shown in Equation 2, are use to construct the dynamic meta-analysis computations. Thus, each category has its own first order differential equation, which includes the effects of each interaction as well as the category time point (or in the case of a feasibility study, a time constant). Each interaction gain coefficient (B) in Equation 2 is simply the change in the affected interaction measure divided by the time point (or in the case of a feasibility study, the category time constant). Because the effect of time is included, the dynamic meta-analysis can predict outcome measures at multiple time points over the entire disease course. Thus, a dynamic meta-analysis can be "simulated" much like a traditional mechanistic model. Because the time-based differential equation computations of dynamic meta-analysis are inherently more complicated than the algebraic regression equations of traditional meta-analysis, the use of a computer simulator assists in

its implementation. For this feasibility study, the dynamic meta-analysis was coded, simulated, and analyzed in Matlab (Mathworks, Inc.).

2.10 Post-result analysis and prediction

The basic results of dynamic meta-analysis are quantitative predictions of each outcome measure or category outcome measure changes over time. Additional, higher level results can be obtained by performing sensitivity analyses, which perturb the system and measure the resulting affects. Perturbation can include varying the initial conditions of each category individually or en masse, or varying the interaction gain coefficients (B). Changing initial conditions provides an assessment of the effect size whereas varying specific or category gains provides an assessment of their sensitivity/specificity. For more detail on sensitivity analyses, see (Mitchell, Feng et al. 2007; Mitchell and Lee 2007; Mitchell and Lee 2009).

Traditional meta-analysis analytical tools, such as statistical linear regression and effect size prediction, are still useful to analyze dynamic meta-analysis results. However, the dynamic and multi-variate nature of dynamic meta-analysis also provides possibilities for richer analyses like those typically seen in the analysis of complex or dynamical systems. Given that the two greatest advantages of dynamic analysis are the implicit inclusion of interactions and explicit inclusion of time, analyses that examine how relationships change over time are particularly telling. Analyses such as cross-correlation (or landscapes) of outcome measures or category outcome measures at specific disease time points, such was done in (Mitchell and Lee 2008) and (Mitchell and Lee 2007), provide a overview of what the system is doing without becoming mired in detail.

Finally, the implicit inclusion of interactions allows combination treatments to be examined. All clinical treatments, in some form, exploit a cellular interaction at some level. For example, pharmaceutical modulators typically exploit the interaction between a receptor and its ligand. Thus, every potential interaction within the dynamic meta-analysis structure can be evaluated as a hypothetical treatment possibility. Furthermore, the structure of dynamic meta-analysis allows every single interaction (whether between outcome measures or between categories of outcome measures) to be varied and simulated individually and in combination. Measuring the resultant effect size of an interaction or combination of interactions predicts its potential treatment efficacy. For more methodological detail on simulating combination therapies, see our previous work with combination treatments and spinal cord injury (Mitchell and Lee 2008).

3. Results of a G93A SOD1 feasibility study

We begin by examing the effect size of each category, an analysis that is typically seen with traditional meta-analysis. Table 3 reveals the average, standard deviation, maximum, and minimum effect size of each category based on a sensitivity analysis that perturbed the intial conditions. Note that "N" is the connectivity, or number of interactions (as shown in Figure 1), affecting the category measure. This examination reveals that the average effect of, for example, treating energetics is a relatively unimpressive 19% outcome change for a 100% treatment effect on energetics itself. (Note that a "real" treatment would have effects substantially smaller than 100%, often only 10% or so.). However, this type of analysis misses the potential for interactions completely and to some extent even minimizes the potential significance of targeted treatments by averaging.

Category	Avg	Stdev	Min	Max	N
Axon Transport	-1%	12%	-21%	16%	6
Chemistry	11%	27%	-6%	71%	7
Energetics	-19%	71%	-98%	102%	7
Excitotoxicity	0%	39%	-80%	36%	7
Free Radical	2%	24%	-53%	44%	10
Genetics	3%	6%	-3%	12%	5
Inflammation	14%	21%	-6%	49%	7
Necro-Apoptosis	16%	26%	-35%	59%	10
Proteomics	13%	24%	-17%	56%	8
Systemic	-2%	5%	-10%	2%	5

Table 3. Standard meta-analysis result table illustrating the effect of each category on disease outcome measures (survival and function).

3.1 Dynamics of the G93A SOD1 mouse pathology

Next, we examine the relative changes in the category outcome measures over time in order to get a better feel of the system dynamics. As shown in Figure 4, initially, the system exhibits a period of relative quiescence (days 0-80) in which there appears to be little variation from the baseline operating point. However, closer examination reveals a few fluctuations, which appear as small oscillations from baseline (Figure 5). Over time each oscillation grows in magnitude, with the first notable oscillation starting around day 40. However, the component trajectories do eventually explode at approximately day 150.

These qualitative system features of ALS align well with the characterization of the G-93A SOD-1 experimental paradigm. In fact, the first large oscillation corresponds to the average onset of measurable functional deficits and the final explosion aligns with the average time of death for the G-93A SOD-1 mouse model (Xu, Jung et al. 2004; Kieran, Hafezparast et al. 2005; Gould, Buss et al. 2006; Teuchert, Fischer et al. 2006). It should be noted that the oscillations of this system do not necessarily represent the relapsing and remitting of functional deficits, such as is seen with multiple sclerosis, but rather the oscillations of individual mechanisms and pathways. In fact, such oscillations could be responsible for small fluctuations sometimes seen within and among mechanistic studies, such as those examining axonal transport (De Vos, Chapman et al. 2007) and protein aggregation (Stieber, Gonatas et al. 2000; Gould, Buss et al. 2006). How oscillations correlating with specific losses in muscle function remains to be seen. It is likely that the overall loss of systemic control aligns with what is typically seen as continuously degenerating function or degenerative function with intermixed plateaus.

From a system dynamics point of view, it is likely that the exploding oscillations of ALS are the result of an unstable system. Initially, the regulatory systems, including excitability, ionic and axonal transport, cellular energetics and others, are able to maintain partial control, as evidenced by the smaller oscillations, which are an attempt to regulate. However, as the disease progresses the control mechanisms simply fail to keep up.

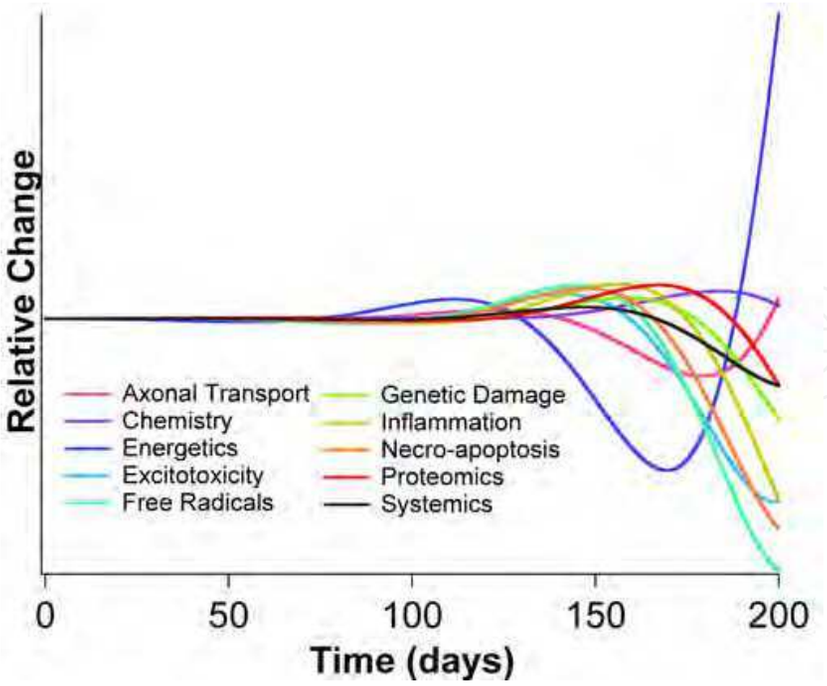

Fig. 4. Unstable, oscillatory dynamics of ALS predicted by dynamic meta-analysis .

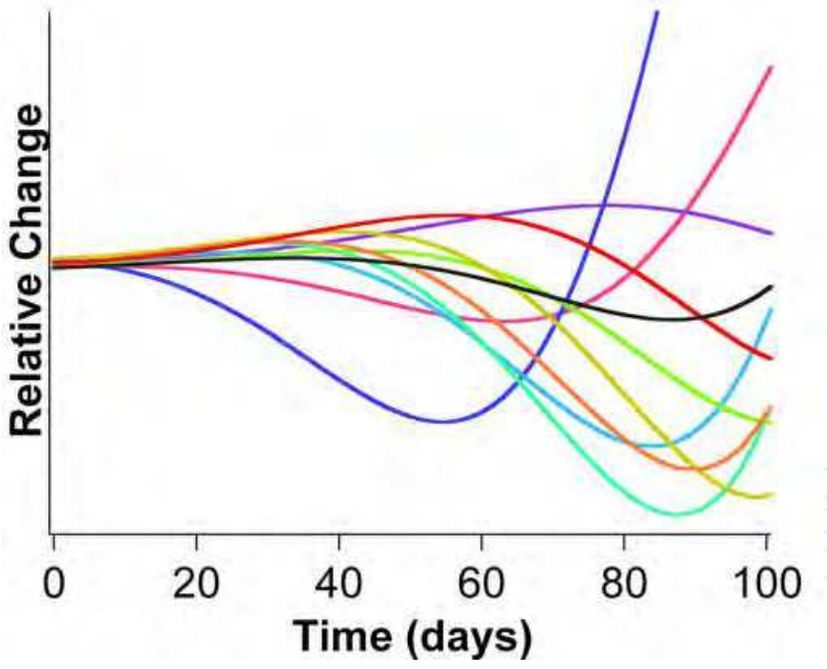

Fig. 5. Expansion of oscillations initiating during the pre-symptomatic quiescent period.

3.2 Combination therapy predictions

We examine how hypothetical therapeutics that exploit single and multi-category interactions can potentially "treat" the system. We utilize the systemic category as our primary outcome measure since it includes known functional metrics. Two different combination treatment types are examined: 1.) combination treatments that stabilize the system (e.g. dampen the oscillations) and 2.) synergistic combination treatments.

Stabilizing Treatments: If pathological progression is driven by, or is the result of, system instability, then one potential therapeutic strategy is to develop treatments that rectify the instability. We tested single treatments that targeted individual category interactions as well as combination treatments that simultaneously targeted up to 3 category interactions. A small percentage of the over 44,000 different combinations treatments investigated rectified the system instability (See example in Figure 6), thereby preventing the "explosion" typically seen between days 150-200 at the average time of death. That is, these treatments have the potential to greatly extend the life span of the typical G-93A mouse.

Of note is that many of the most successful treatment combinations did not include the component that was responsible for the initiating perturbation. Also in some cases, the directions (sign of the relationship) that components best treated the system could be non-intuitive, again likely owing to the highly interactive nature of the ALS system.

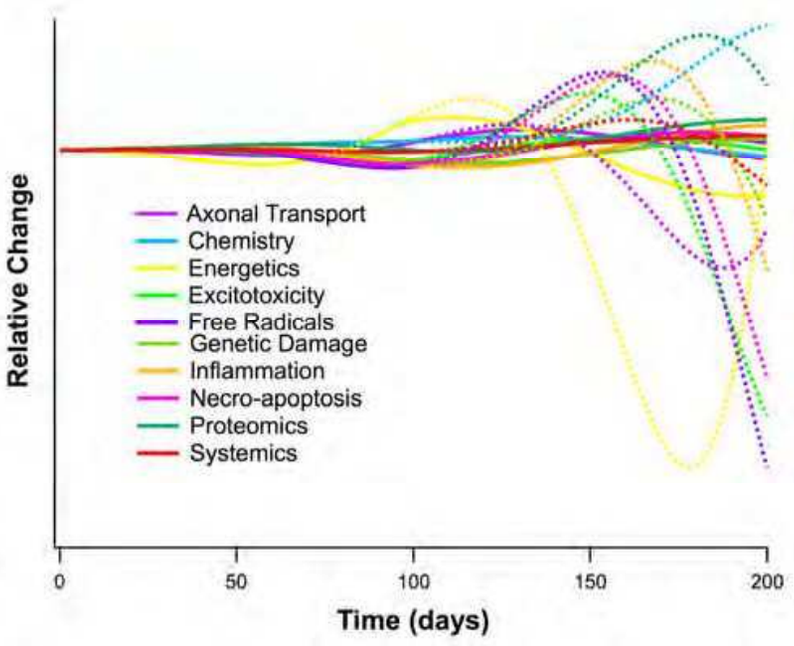

Fig. 6. Dynamics of ALS predicted by dynamic analysis of the G93A SOD1 mouse model. ALS dynamics are unstable, (dashed lines) characterized by growing oscillations that "explode" near the average time of death. Dynamic meta-analysis of potential treatment combinations predicts that a small percentage of 3-way treatment combinations can assist in re-stabilization of the system (solid lines).

Treatment synergism: Whether stabilizing or not, or just purely interaction-based, many of the ALS treatments have a synergistic effect. That is, their combined effects are substantially greater than the sum of their individual effects. For two-way treatments (treatments addressing two category interactions), 16% of the total possible 10,000 combinations are synergistic. (Note that treatment direction was made in the more favorable direction.) For three-way combinations, approximately 22% of the possible 900,000 combinations are synergistic (Figure 7).

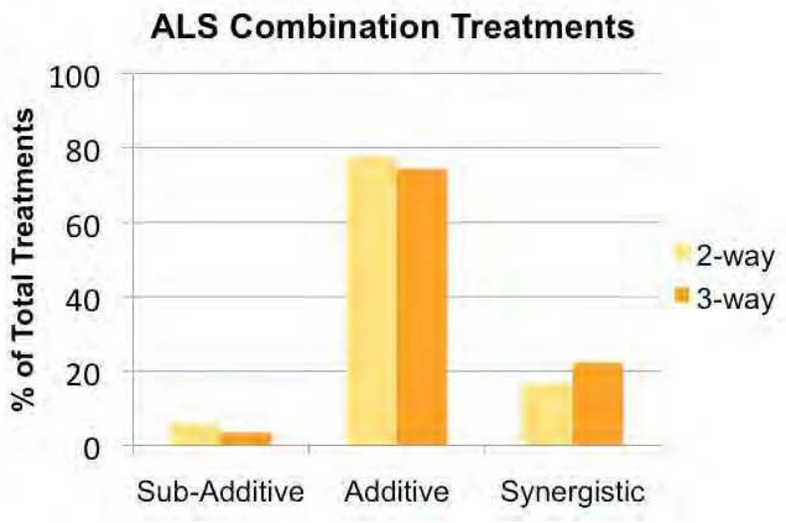

Fig. 7. Percentage of total treatment combinations belonging to each efficacy type.

Tables 4 and 5, show the efficacies of 2-way and 3-way synergistic combination treatments. A linearly additive treatment (combination A&B effect = A effect + B effect) was assigned an efficacy factor of 1.0. Thus, synergistic treatments have efficacy factors >1 and sub-additive treatments have efficacy factors <1. Therefore, categories with higher average and maximum efficacy factors have a tendency to produce greater synergistic effects in combination.

Category	Avg	Stdev	Max	Count
Axonal Transport	1.08	0.16	1.74	59
Chemistry	1.02	0.05	1.39	107
Energetics	1.23	0.32	2.44	229
Excitotoxicity	1.09	0.24	2.33	160
Free Radical	1.06	0.14	1.93	311
Genetics	1.01	0.02	1.21	86
Inflammation	1.03	0.07	1.66	195
Necro-Apoptosis	1.10	0.23	2.35	327
Proteomics	1.04	0.15	2.05	154
Systemic	1.05	0.07	1.23	22

Table 4. Synergistic two-way combination treatment predictions.

Category	Avg	Stdev	Max	Count
Axonal Transport	1.08	0.17	2.82	17395
Chemistry	1.19	0.26	4.85	23101
Energetics	1.09	0.19	2.82	22332
Excitotoxicity	1.05	0.13	2.13	33020
Free Radical	1.04	0.12	2.01	12929
Genetics	1.05	0.12	3.26	22589
Inflammation	1.09	0.19	2.67	35586
Necro-Apoptosis	1.09	0.20	2.60	22603
Proteomics	1.06	0.14	2.05	11322
Systemic	1.00	0.00	1.00	0

Table 5. Synergistic three-way combination treatment predictions.

4. Conclusions

System dynamics revealed. Conventional wisdom in ALS research has been that there is a single, specific root cause. However, dynamic meta-analysis predicts that a system-level instability is the actual problem (see oscillations in Figure 4). Lending credence to the predictions of dynamic meta-analysis is the mounting evidence from recent studies that indicates that multiple mutations or underlying mechanisms can result in the symptoms characterized as ALS (Rothstein 2009).

Novel treatment strategies identified. In this small scale feasibility study of ALS, dynamic meta-analysis predicts that reducing the overall feedback gain will be more effective than identifying and ameliorating a single "source" or point of initiation (Mitchell and Lee 2010). That is, inducing small changes across multiple categories of mechanisms is more effective than inducing a large change in a single category. Additionally, treatments that target the underyling system dyanmics, such as stabilizing oscillations, could be another potentially effective path.

Combination treatment prediction enabled. Another key opportunity afforded by dynamic meta-analysis is an innovative approach to predicting combination treatment effectiveness in a high-throughput manner. The interacting differential equations of dynamic meta-analysis implicitly include all possible treatment interactions. Thus, potential synergistic combinations can be identified before they are explicitly examined experimentally. For example, in spinal cord injury, a sweep of all possible combinations of virtual treatments revealed that none were synergistic (Mitchell and Lee 2008). While disappointing, we were at least able to discover treatments that combined linearly. On the other hand, in our initial evaluation of ALS, a small percentage of treatment combinations show very profound synergism! It appears that in ALS, the broader the treatment the more effective it becomes. (Figure 6 illustrates an example of a 3-way combination that appears to arrest the oscillatory explosion observed in the control case.) Finally, dynamic meta-analysis is not only well suited to identify promising combinations but can be used to prioritize them as well.

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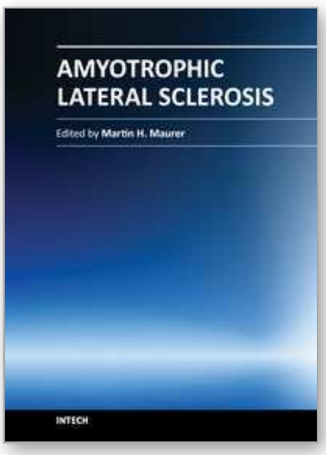

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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