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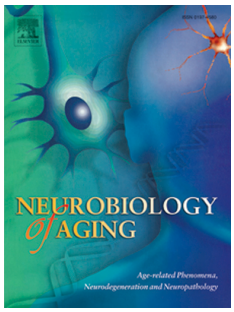

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A quantitative model of human neurodegenerative diseases involving protein aggregation

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Abstract

Human neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Amyotrophic lateral sclerosis involve protein aggregation and share many other similarities. It is widely assumed that the protein aggregates exhibit a specific molecular mode of toxic action that propagates by molecular contact (seeding). This paper presents a simple mathematical model arguing that these diseases are caused by reduced energy available after subtracting cell maintenance due to general turnover of the misfolded proteins, rather than a specific toxic molecular action of the protein. Proteomic cost minimization can explain why highly expressed proteins changed less during evolution, leaving more energy for reproducing microorganisms on longer evolutionary timescales. In higher organisms, the excess energy instead defines cognitive capability, and the same equations remarkably apply. Proteomic cost minimization can explain why late-onset neurodegenerative diseases involve protein aggregation. The model rationalizes clinical ages of symptom onset for patients carrying pathogenic protein mutations: Unstable or aggregation-prone mutations confer a direct energy cost of turnover, but other risk modifiers also change the available cellular energy as ultimately defining clinical outcome. Proteomic cost minimization is consistent with current views on biomarker histories, explains conflicting data on overexpression models, is consistent with energy cost tradeoffs causing compensatory hyperconnectivity during early disease, and is supported by specific experiments showing that proteasome activity is required to confer toxicity to pathogenic mutants. The model lends promise to a quantitative personalized medicine of neurodegenerative disease.

Keywords: Protein misfolding, proteasome, proteostasis, energy, neurodegeneration

1. Introduction

Evolution is the fundamental process that has shaped proteomes by randomly mutating DNA and, by random drift or active selection, fixating some mutations in the populations(Hurst, 2009; Presgraves, 2010). The most prominent relationship of proteomics is that proteins that are highly expressed (i.e. featuring high copy numbers in cells) are more evolutionary conserved in prokaryotes(Sharp, 1991) and eukaryotes(Pál et al., 2001), including mammals(Jordan et al., 2004; Zhang and Li, 2004). This so-called expression-rate (ER) anti-correlation shows that the abundance of proteins in a cell is somehow particularly important during the course of evolution(Drummond et al., 2005; Pál et al., 2001). Proteins also tend to use synthetically cheaper (in terms of ATP) amino acids in all kingdoms of life(Seligmann, 2003; Wagner, 2005).

Apparently unrelated to this, millions of people worldwide suffer from age-induced neurodegenerative diseases associated with large deposits of aggregated proteins(Bucciantini et al., 2002; Soto and Pritzkow, 2018). In Alzheimer's disease (AD), the so-called senile plaques consist mainly of regular β-sheet fibrils of the infamous β-amyloid peptide (Aβ); in Parkinson's disease (PD), the Lewis bodies are made up of the protein α-synuclein; in amyotrophic lateral sclerosis (ALS) the deposits consist of superoxide dismutase 1 (SOD1)(Andersen, 2006). Consensus is establishing that these deposits are typically not pathogenic (although toxic) but that soluble protein oligomers inside the cells may attain a pathogenic molecular mode of action. The many histopathological and clinical similarities of these diseases (protein deposits, age-triggering, oxidative stress associated, neurodegenerative) imply a common pathogenesis of protein misfolding(Bucciantini et al., 2002; Gan et al., 2018).

Although protein aggregation is cytotoxic and potentially related to disease(Brouillette et al., 2012; Bruijn, 1998; Pauwels et al., 2012; Tiwari and Kepp, 2015), the cellular pathogenic mechanism is unknown and not yet understood(Cook et al., 2012; Dobson, 2003; Eisenberg and Jucker, 2012; Hardy and Selkoe, 2002; Knowles et al., 2014). Efforts to identify and target the supposed malicious protein aggregates and oligomers with inhibitors or antibodies have so far met with clinical failure(Chiti and Dobson, 2017; De Strooper and Chávez Gutiérrez, 2015; Gregersen et al., 2006; Herrup, 2015; Karran and Hardy, 2014; Kepp, 2017). This begs the question whether we miss a key determinant of disease course, and it is widely debated whether the protein aggregates in any particular shape and size are the root cause of disease or merely a side effect or contributing feature(Bucciantini et al., 2002; Herrup, 2015; Kepp, 2017, 2016).

A central question is how protein misfolding causes the clinical phenotype of neurodegeration. It is widely assumed that the misfolded proteins are pathogenic themselves by specific molecular interaction *in vivo* that can be “seeded” or “infectious” in the form of prions in the same way as seen in aggregation assays (Chiti and Dobson, 2017; Hardy, 2006; Soto and Pritzkow, 2018). The mutations, due to their penetration and common dominant inheritance, are often though to gain a toxic function(De Strooper et al., 1998; Stathopulos et al., 2003; Wang et al., 2008), although a loss of natural function is also debated for these proteins(Kepp, 2016; Saccon et al., 2013; Saura et al., 2004; Shen and Kelleher, 2007), and the introduction of new misfolded proteins can overwhelm the existing proteostasis(Gidalevitz et al., 2006), and some protein misfolding diseases may be transmitted (prion diseases and controversially suggested, AD(Jarrett and Lansbury, 1993; Jaunmuktane et al., 2015)).

Although many suggestions have arisen(Götz et al., 2011), a specific molecular mechanism that explains clinical disease has not been identified, and accordingly there are no causative treatments available. Focus now centers on the intracellular oligomers that precede the fibrils; these oligomers are soluble and more toxic to cultured cells than fibrils(Götz et al., 2011; Ono et al., 2009; Walsh et al., 2002). The oligomers are targeted without actually knowing their bioactive structure, exact location, and the pathogenic process in which they are involved. They interact with many other molecules and cell parts, preventing the identification of a single pathogenic mode of *in vivo* action(De Strooper, 2014; Karran and Hardy, 2014). Efforts to reduce the production of the misfolding proteins by inhibitors or reduce oligomer activity by antibodies, which work in simpler tests, have failed to benefit the human patient, leading to calls for new causal disease mechanisms(De Strooper and Chávez Gutiérrez, 2015; Herrup, 2015; Kepp, 2017; G. P. Morris et al., 2014).

2. The model of proteomic cost minimization

The model of proteomic cost minimization as a basis for protein evolution(Kepp and Dasmeh, 2014) is briefly reviewed below. The E−R anti-correlation has been explained(Drummond and Wilke, 2009, 2008) as a selection against inefficient translation leading to misfolded proteins. Highly expressed proteins would then be under a stronger selection pressure since the copy number of misfolded proteins U_i scales with the total abundance of the protein A_i. An empirical equation for the fitness cost Φ_i has thus been suggested(Drummond and Wilke, 2008):

$$\Phi_i \propto \exp(-cU_i) \quad (1)$$

In this equation, *c* is an unknown dimensionless fitness cost constant of one misfolded protein.

To understand this observation at the molecular level, we first introduce a simplified protein turnover scheme, which provides the timeframe of the problem. The proteostasis of any protein *i* can be written in a simplified way as(Kepp and Dasmeh, 2014):

$$mRNA_i \xrightarrow{k_{s_i}} F_i \underset{k_{2_i}}{\overset{k_{1_i}}{\rightleftharpoons}} U_i \xrightarrow{k_{d_i}} D_i \quad (2)$$

In this scheme, F_i represents the folded protein copies within the cell, U_i represents misfolded protein copies, and D_i are degraded chemical products, with the rate constants of each step annotated. k_{d_i} is the rate constant (in units of protein molecules per second) for degradation of the misfolded protein copies. Since many values of degradation rate constants of proteins are known, we also know that the values of k_{d_i} vary greatly with the protein *i*.

We now introduce an estimate of U_i assuming that the misfolded protein arises from a simple two-state folding process. If so, we have:

$$U_i = A_i \left(\frac{1}{1+\exp\left(\frac{-\Delta G_i}{RT}\right)} \right). \quad (3)$$

A_i represents the total copy number of the protein within the cell, ΔG_i is the folding stability (measured as a negative number in kJ/mol) of this protein and *RT* is the thermal energy of the cell at 37°C. In the limit of infinite protein stability ($\Delta G_i \rightarrow -\infty$), $U_i \rightarrow 0$. The cellular maintenance energy (in J s^{-1}) allocated to one protein *i* per time unit can then be derived as(Kepp and Dasmeh, 2014):

$$dE_{m,i}/dt = A_i \left(\frac{1}{1+\exp\left(\frac{-\Delta G_i}{RT}\right)} \right) k_{d_i} N_{aa_i} (C_{s_i} + C_{d_i}) \quad (4)$$

N_{aa_i} is the number of amino acids in protein *i*, whereas C_{s_i} and C_{d_i} represent the average synthetic and degradation cost (in units of J) per amino acid in protein *i*(Kepp and Dasmeh, 2014).

Equation (4) is for one protein. Let us now write the *total* protein turnover cost per time unit is the sum of the turnover costs of all proteins within the cell:

$$dE_m/dt = \alpha \sum_i dE_{m,i}/dt = \alpha \sum_i A_i \left(\frac{1}{1+\exp\left(\frac{-\Delta G_i}{RT}\right)} \right) k_{d_i} N_{aa_i} (C_{s_i} + C_{d_i}) \quad (5)$$

Energy costs are seen to scale with A_i. Copy numbers A_i vary greatly with the type of protein i (typically from zero to 10^6) and thus some proteins are substantially more systemically important to the energy state as explained by Equation (5). We have included the possibility that the activity of protein turnover affects the total cost by a constant representing an effective concentration of proteases as determining the activity of the proteasome, called α in Equation (5). This constant multiplies with k_{d_i} and thus scales the energy cost per time unit.

The energy cost per time unit of the proteome, Equation (5), explains the E-R correlation: One first assumes that the fitness is given by the energy available for reproduction dE_r/dt after subtracting the energy cost of Equation (5) (ignoring non-proteome energy costs) from the total produced energy of the cell dE_t/dt:

$$\Phi_i = dE_r/dt = \ dE_t/dt - dE_m/dt \quad (6)$$

In the simple case where the total energy production is constant, minimization of dE_m/dt maximizes fitness. From Equation (4), fitness (and hence the selection coefficient) scales with the abundance of the protein. Accordingly, abundant proteins are under stronger selection pressure for cost minimization, making them less likely to accept random (on average destabilizing) mutations and thus conserving them more over evolutionary time, as measured by a smaller probability of fixation and evolutionary rate. Because the exponential of Equation (1) can be expanded as $1- cU_i$ due to the small values of cU_i, this theory recovers and explains the phenomenological fitness cost constant c of Equation (1) in terms of fundamental protein turnover parameters(Kepp and Dasmeh, 2014).

Among costly processes, protein synthesis accounts for ~30% of resting energy expenditure in man(Reeds et al., 1985; Waterlow, 1995) and typically ~75% in growing microorganisms(Harold, 1987). Typical costs are ~10 kJ per gram protein, at about 3-5 grams of protein produced per kg mass per day(Waterlow, 1995). A typical adult human thus synthesizes 200-300 grams of protein per day, spending 2000-3000 kJ on this process alone per day out of a total basic metabolic rate of perhaps 6000 kJ/day[3]. Protein degradation may cost another 20% of the mammalian total energy expenditure(Fraser and Rogers, 2007), making protein turnover the most energy-consuming process of the body.

3. Energy model of neurodegenerative disease

In the following, the fitness function of Equation (6) is argued to also describe a cognitive status function of the brain. Equation (6) defines the energy available after subtracting maintenance costs from the produced energy. Whereas microorganisms spend most of their surplus energy on reproduction, higher organisms use a large part (~20%) of their surplus energy for cognition and brain function (Ames III, 2000; Attwell and Laughlin, 2001; Bélanger et al., 2011; Raichle and Gusnard, 2002). In higher organisms, we can then consider dE_r/dt as energy available for cognitive execution, dominated by the ~50% energy spent on the ion pumps(Engl and Attwell, 2015; Raichle and Gusnard, 2002). To distinguish it, we call it dE_x/dt:

$$\frac{dE_x}{dt} = \frac{dE_t}{dt} - \alpha \sum_i A_i \left(\frac{1}{1+\exp\left(\frac{-\Delta G_i}{RT}\right)} \right) k_{d_i} N_{aa_i} (C_{s_i} + C_{d_i}) \qquad (7)$$

In this simplest model, the energy available for cognition has been reduced to a function only of proteome turnover costs, summed over all proteins i. Of course, other costs can easily be included in such a model, but the purpose at this point is to show how protein misfolding relates to the clinical outcome, which we take as dE_x/dt. Thus, any impairment of dE_x/dt caused either by a reduction in dE_t/dt or an increase in maintenance energy dE_m/dt will reduce cognitive capacity.

From Equation (7), any protein of large abundance A_i or turnover constant k_{d_i}, low stability, or high specific synthesis and degradation costs $C_{s_i} + C_{d_i}$will be particularly expensive to the cell, all else being equal. Pathogenic mutation can change several of these parameters, most commonly the stability. Please note that the bias towards synthetically cheap amino acids seen in real protein sequences(Heizer et al., 2006; Seligmann, 2003; Wagner, 2005) is largely reflected in the parameter C_{s_i}, and, like stability, reflects an optimum that can be disturbed according to Equation (7) by pathogenic mutation. Many other risk factors can be expected to influence either dE_m/dt or dE_t/dt. A summary of this mechanism of neurodegeneration is given in **Figure 1**, with energy status being the central determinant of cell fate and cognitive capacity.

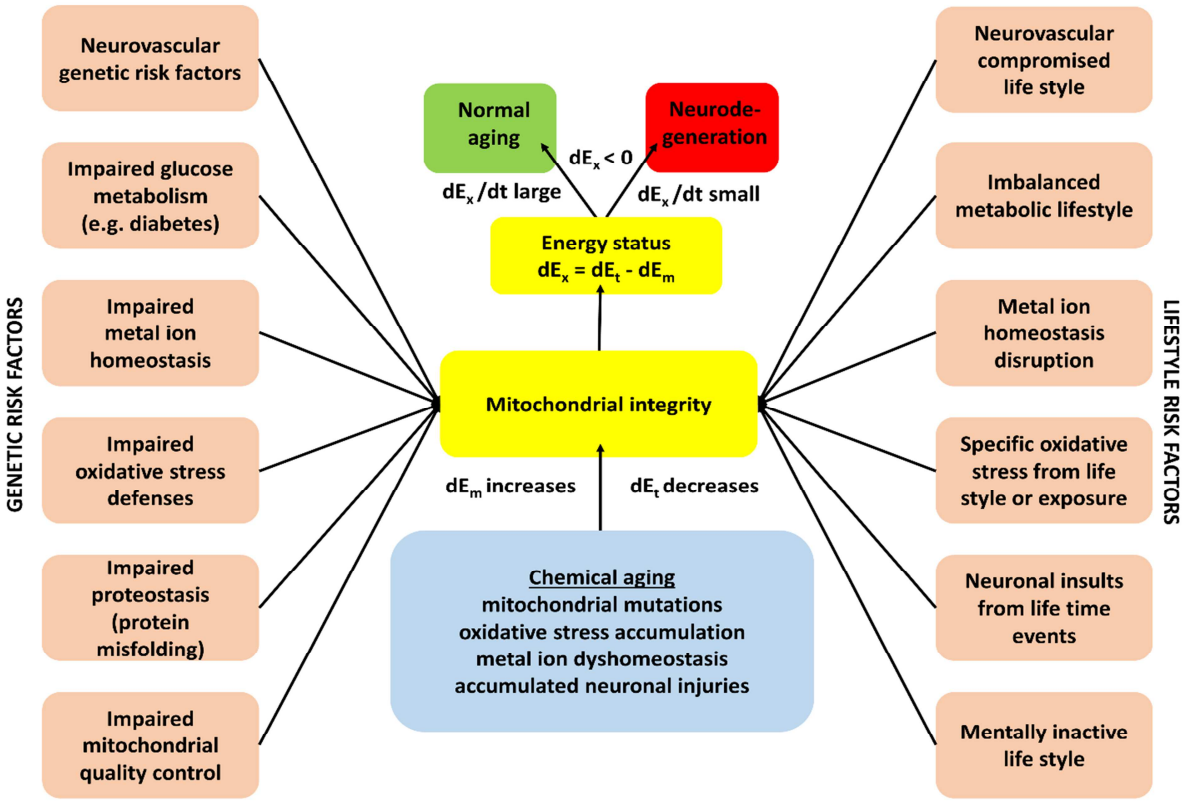

Figure 1. Summary of the exhaustion mechanism of neurodegeneration. Genetic and life style risk factors affect the energy balance of the brain by elevating maintenance costs (dE_m) or lowering total energy production (dE_t). If the process occurs gradually, normal aging is observed. If the process is accelerated, the cost of maintenance will increase faster than the ability to compensate energy loss, leading to neurodegeneration when $dE_m \sim dE_t$.

Energy production likely decreases with age and the energy needed for maintenance increases with age, as seen from the increase in maintenance and stress-related proteins in the aging human brain(Lu et al., 2004), particular changes in AD(Liang et al., 2008), and from the glucose biomarkers(Bateman et al., 2012; Dunn et al., 2014). To understand this, we first assume that the deceleration in energy production and the acceleration in maintenance costs are constant over time. If so we have:

$$\frac{dE_t}{dt} = \left(\frac{dE_t}{dt}\right)_0 - C_t t \quad (8)$$

$$\frac{dE_m}{dt} = \left(\frac{dE_m}{dt}\right)_0 + C_m t \quad (9)$$

Here, C_t and C_m are the constants of change in the energy production and maintenance costs per time unit, respectively. Accordingly:

$$\frac{dE_x}{dt} = \left(\frac{dE_t}{dt}\right)_0 - \left(\frac{dE_m}{dt}\right)_0 - (C_t + C_m)t \quad (10)$$

Thus, the energy available for cognition is a function of four variables: The genetically encoded starting rates of energy production and maintenance, and the specific constant changes in these two processes:

$$C_t = \frac{d^2E_t}{dt^2} \quad \text{and} \quad C_m = \frac{d^2E_m}{dt^2} \quad (11)$$

The model is shown in **Figure 2A-C**, using a healthy normality index of 100, with a 50% cost of total energy devoted to maintenance at t = 0. Because of the constant changes in energy production and maintenance, linear changes are seen in dE_t/dt, dE_m/dt, and accordingly, dE_x/dt. The disease (but not necessarily symptom) age of onset is defined as the point of intersection where dE_x/dt = 0 (dashed lines). The simplest loss of function phenotype would manifest as a larger C_t, the reduction rate of the energy production, whereas the simplest gain of function mechanism would accelerate maintenance costs, C_m. Mixtures of these situations are possible. These two situations correspond to **Figure 2B** and **2C**, where values of C_m = 0.5 and C_t = 0.5 have been used respectively, whereas in the "normal" case of **Figure 2A**, C_m = 0.25 and C_t = 0.25. The approximate relationship $dE_m/dt \sim dE_x/dt \sim \frac{1}{2}\, dE_t/dt$ holds for a normal brain(Engl and Attwell, 2015; Raichle and Gusnard, 2002).

The age of clinical symptom onset is defined as the time where the energy available for cognition becomes zero, $dE_x/dt = 0$:

$$t_{onset} = t \mid \frac{dE_t}{dt} = \frac{dE_m}{dt} \quad (12)$$

This situation can importantly be modeled as simple constant acceleration as seen in **Figure 2A-2C**. In this simple case, the age of clinical onset simply becomes:

$$t_{onset} = \frac{\left(\frac{dE_t}{dt}\right)_0 - \left(\frac{dE_m}{dt}\right)_0}{(C_m + C_t)} \quad (13)$$

The parameters are the average values for the full cells of the affected cell types. Clinical age of onset depends on the basic energy production and maintenance costs, modified by the

accelerated costs and decelerated energy production during aging. All four terms can vary between individual patients as a function of risk modifiers.

Let us for clarity consider the situation where the patient has normal energy production throughout life but constantly accelerating maintenance costs. This case is shown in **Figure 2B**, and the energy available for cognition per second is described as:

$$\frac{dE_x}{dt} = \left(\frac{dE_t}{dt}\right)_0 - \left(\frac{dE_m}{dt}\right)_0 - C_t t - \frac{d}{dt}\alpha \sum_i A_i \left(\frac{1}{1+\exp\left(\frac{-\Delta G_i}{RT}\right)}\right) k_{d_i} N_{aa_i} (C_{s_i} + C_{d_i}) t \qquad (14)$$

The case in **Figure 2B** represents increased C_m. Several of the parameters in Equation (14) can be time-dependent. For example, the amount of misfolded protein may increase due to destabilization caused by oxidative stress other forms of chemical aging. Proteins that are easily and quickly degraded (large k_{d_i}) pose a particular challenge to the maintenance costs, but in proportion to their abundance. Thus, the combination of abundant and quickly degraded proteins is the most severe problem in Equation (14).

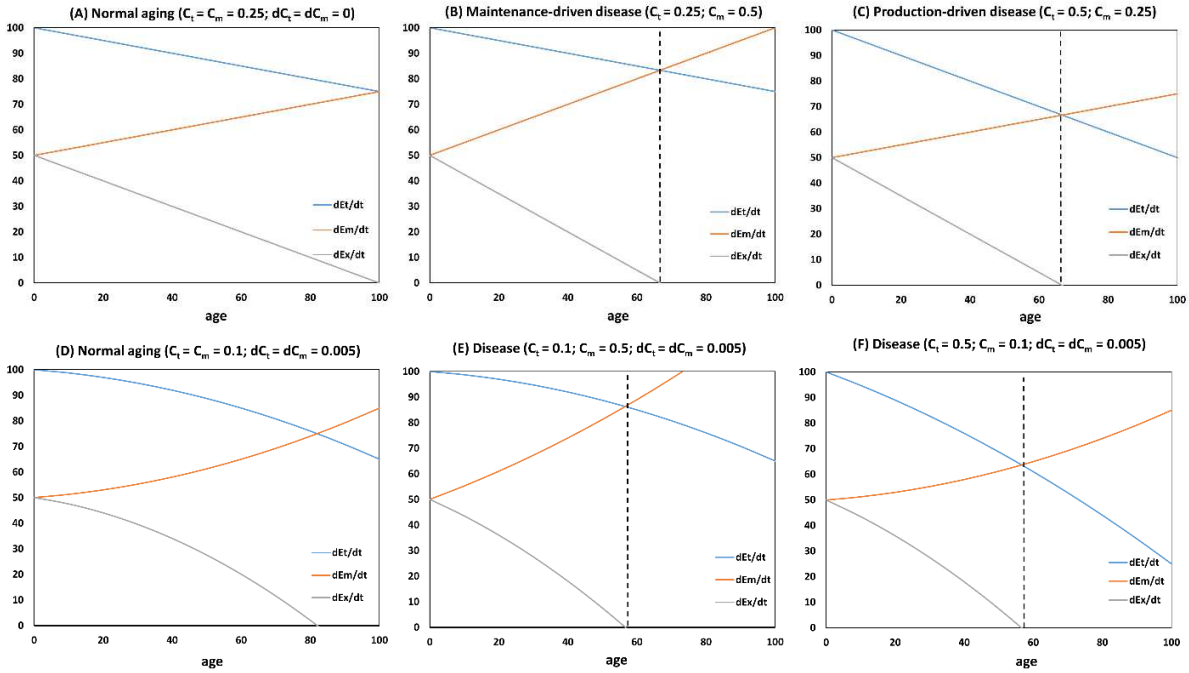

Figure 2. Six scenarios of proteomic cost driven neurodegenerative disease. **(A)** Normal aging with constant changes in energy production and maintenance ($C_t = C_m = 0.25$; $dC_t = dC_m = 0$); **(B)** disease driven by increased maintenance costs ($C_t = 0.25$; $C_m = 0.5$; $dC_t = dC_m = 0$)**; (C)** disease driven by reduced energy production ($C_t = 0.5$; $C_m = 0.25$; $dC_t = dC_m = 0$); (**D**) model of accelerated aging ("viscous cycle") where the rate of change varies ($dC_t = dC_m = 0.005$) for a normal person ($C_t = C_m = 0.1$); (**E**) as in (**D**) but with $C_m = 0.5$; (**F**) as in (**D**) but for a patient with $C_t = 0.5$.

The model can estimate the clinical age of onset of carriers of familial disease mutations as a function of the severity of a protein mutant. For example, SOD1 mutants causing FALS generally exhibit reduced stability or net charge, which both work to increase the misfolding and turnover of this important and abundant (high A_i) protein(Lindberg et al., 2005; Wang et al., 2008; Zetterström et al., 2007). In the model, the increased cost of maintaining the larger pool of misfolded mutant SOD1 copies causes motor neurons to have less energy available for execution, when total energy budgets become stressed (**Figure 2B**). Typical SOD1 mutants reduce ΔG_i by 5-10 kJ/mol(Furukawa and O'Halloran, 2005; Khare et al., 2006; Vassall et al., 2006). A typical decrease ΔG_i of 5 kJ/mol will double the copy number of misfolded proteins in

the cell (Equation 3) regardless of the abundance, and in any reasonable range of ΔG_i (-20 to -100 kJ/mol) so this effect is very generic. The last part of equation (14) measures the total C_mt for the cell; a doubling of cost of the specific cost of an abundant protein with A_i = 100,000 copies would increase in total dE_m by 1% (**Figure 2B**).

Let us study another scenario where C_m and C_t increase with time, due to accelerating turnover costs per time. The mechanistic basis is that lack of energy can affect other features such as depolarization of neurons, excitotoxicity, calcium imbalances, additional costs of rewiring neuron connections, and oxidative stress that may feed back and aggravate the continuous loss of dE_x/dt (Beal, 1995). **Figure 2D-2F** shows the model where the change in maintenance cost accelerates with aging to produce non-linear, accelerated disease progressions. Even a small acceleration of the maintenance costs can move clinical symptom onset to much earlier age. Mutations that increase turnover costs increasingly with chemical aging is described by this situation(Eckert et al., 2008; McAuley et al., 2009; Toda et al., 2014; Zhang et al., 2015). Whereas the linear scenario is relatively mild in its impact on the total value of C_m, the non-linear scenario in **Figure 2D-2F** causes disease even at small initial perturbations of the proteostatic machinery.

4. Modeling disease histories and biomarkers

The energy model of neurodegeneration as formulated above implies that disease can be more or less severe, depending on the rate of depletion of energy resources. Many risk modifiers (**Figure 1**) will modulate the real disease history of a patient in a way that may now be modeled. Importantly, even a constant acceleration of dE_m and/or deceleration of dE_t (**Figure 2B and 2C**) will have an *exponential* effect on biomarkers. To understand this, the increasing gap in energy balance (**Figure 2B and 2C right**) will leave more new pathology each time unit, causing an initial exponential buildup of pathology, e.g. non-degraded protein deposits. This buildup will saturate with time as cells die and stop contributing to the pathology. This process is modeled by a logistic function of the pathology (biomarker signal) P:

$$P(t) = \frac{P_{max} P_0 e^{rt}}{P_{max} + P_0 (e^{rt} - 1)} \quad (15)$$

where $r = C_m / (dE_m/dt)_0$ is the rate of pathology buildup, P_0 is the initial pathology signal defined as 1, and P_{max} is the maximal signal defined as 100. Biomarker studies suggest that the

disease progression increases nonlinearly and saturates at long times, giving such a sigmoidal shape(Jack et al., 2010). If C_m is larger according to the model, e.g. due to a highly aggregation-prone protein mutant, r will be larger and cause the sigmoidal curve to be steeper.

Figure 3 illustrates a simple disease history for AD, using the model presented in Equation (15) with $r = C_m / (dE_m/dt)_0 = 0.15$, where C_m can be calculated from the last term of Equation (14). The time of onset of the different signals $P(t)$ has been set as t = 0, 5, 10, 20, 30, and 40, with ranges 1-100 in all cases. Glucose uptake is impaired as the earliest measurable event, followed by Aβ pathology(Jack et al., 2010). A patient with a mutation that produces oligomers subject to intensive proteolysis will exhaust the energy status of the neurons faster than the typical patient; this would lead to an early-onset form of the disease, shifting the age of onset towards the left in **Figure 3**. Thus more severe protein mutants have earlier age of onset because they deplete energy resources faster. At any age, the buildup of pathogenic protein oligomers will accelerate because the energy left for degrading them decreases constantly (**Figure 2B, 2C**). Because these oligomers are in an equilibrium with aggregated deposits, the deposits will increase until saturated when the amount of aggregated protein does not increase further because cell death cancels the new production of aggregates.

The common explanation given for the sigmoidal shape of biomarkers (Jack et al., 2010) is that the shape parallels the *in vitro* aggregation assays, typically monitored by the β-sheet binding thioflavin T, such that an elongation phase is followed by nucleation, leading to an exponential increase is aggregation until saturation. However, in a real neuron, it is very unlikely that this *in vitro* mechanism takes place considering the intracellular concentrations of proteins that will probably only form large aggregates outside the cell, but be constantly degraded as oligomers inside the cell. The model in **Figure 2/3** provides an alternative, systemic explanation for the sigmoidal shape not due to aggregation kinetics but to accelerating energy costs. These two explanations for the observed sigmoidal biomarker histories are fundamentally different and may be tested in the future.

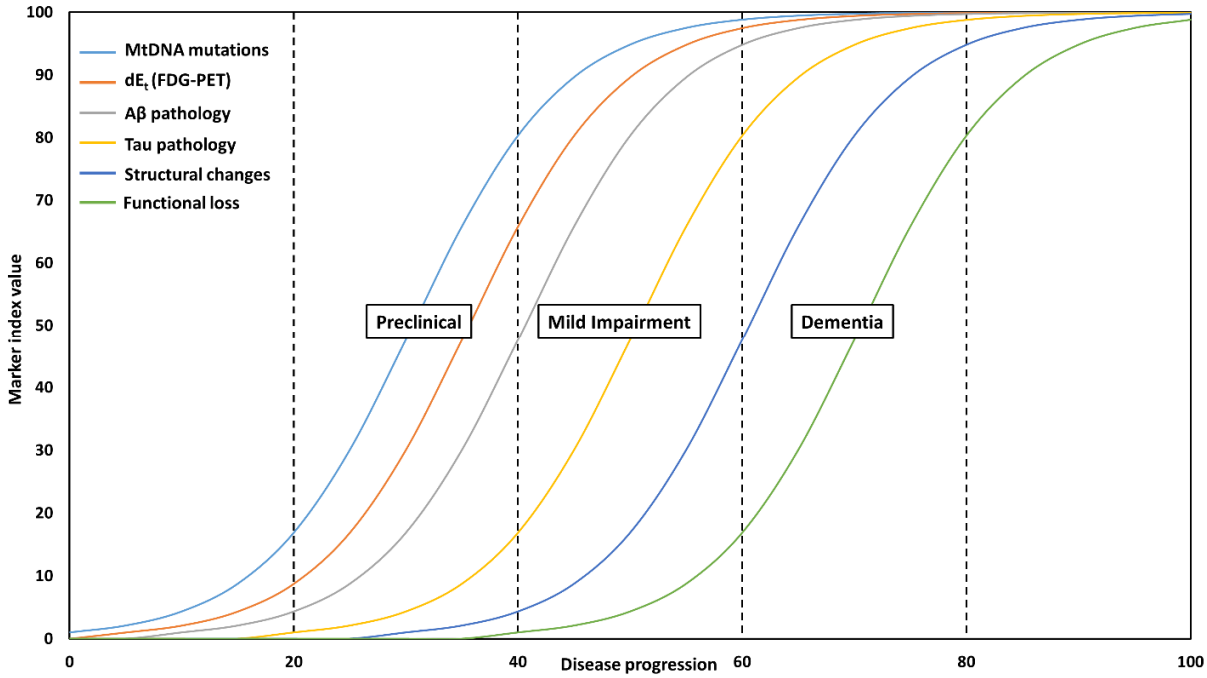

Figure 3. Approximate biomarker normalized index value (0-100) calculated from Equation (15) using r = 0.15, vs. hypothetical disease progression (from 0 to 100) based on a previous model(Jack et al., 2010) as described in the text. Clinical age of onset is chosen as the point of indexed functional loss = 0.15 (in this case approximately 60, separating mild impairment from dementia) and can vary with risk modifiers changing C_m and r, according to Equation (13)-(15).

The model presented here is essentially a single-cell model, yet the crisis of individual cells must somehow propagate to neighbor cells in the brain to cause general neurodegeneration, and multiple cell types are involved. Current views assume that direct molecular seeding causes the spread(Hartl, 2017; Soto and Pritzkow, 2018). The requirement of pathogenic molecules to actually meet each other at the concentrations they operate pose a challenge to the molecular seeding mechanism. To appreciate this, the aggregation seen in vitro typically operates at micromolar concentrations, yet in vivo concentrations of the proteins are typically subnanomolar, i.e. at least 1000-fold lower(Kepp, 2017), raising the questions how these proteins actually meet routinely before being targeted for turnover and how the seeding works between cells.

The energy model described here suggests that disease spread acts via a transfer of energy crisis rather than actual transfer of protein molecules. To understand this better, the

connectivity that underlies the spread of pathology in real tissue has been explored in detail by functional magnetic resonance imaging, showing early long-range hyperconnectivity as a compensatory strategy to counter neurodegeneration(Hillary and Grafman, 2017; Pizzi et al., 2019; Schultz et al., 2017). Compensatory hyperconnectivity is supported many data, e.g. the elevated costs of default mode networks in apoE ε4 allele carriers(Bookheimer et al., 2000; Filippini et al., 2009). The functional connectivity involves the hippocampus where AD typically sets in(Pizzi et al., 2019). The extent of connectivity is a trade-off between improved cognitive capacity by rewiring the synaptic networks and the metabolic costs this rewiring(Hillary and Grafman, 2017). The fact that network connectivity has a metabolic cost contribution to dE_m/dt fits very well to the model described above and suggests that, as energy crisis hits individual cells, their ability to sustain networks (primarily via potentials at the synaptic terminals) are impaired. This weakening of the network then leads to a rewiring to ensure optimal robustness of the overall network, and this comes at an associated *global* energy cost, because the connections are long-range. As energy resources are exhausted in the model (**Figure 2**) low connectivity takes over as more and more cells reach a state of $dE_m/dt = dE_t/dt$.

Thus, the model predicts that protein misfolding diseases spread and become infectious, not because of direct molecular interaction (or "seeding") between proteins copies as widely argued and seen in aggregation assays, but by propagating dE_m/dt upon rewiring of neurons. The controversial claim that Aβ may be infectious as a prion (Jarrett and Lansbury, 1993; Jaunmuktane et al., 2015) can also be viewed via this alternative mechanism.

5. Support for the model: Energy in the healthy brain and in disease

The model provides an answer to the haunting question why neurodegenerative diseases are protein misfolding diseases. A pool of misfolded proteins always exists in all cells but is kept very small, probably below one copy at any instance per cell due to fast turnover. The energy burden and thus disease only manifests in the most energy-requiring cells, including those of the central nervous system. The adult human brain typically uses 20% of the total resting energy, despite weighing only 1200-1500 grams, a few percent of total body mass(Attwell and Laughlin, 2001; Kety, 1957; Magistretti and Pellerin, 1999; Owen et al., 1967). Typically 50% of this brain energy is allocated to maintain the ion gradients central to neuronal signaling, whereas house-keeping takes up the second-largest contribution and includes protein synthesis and degradation

costs(Engl and Attwell, 2015; Raichle and Gusnard, 2002). The neuronal maintenance costs per time unit set the limit on the cognitive abilities via the temporal efficiency of information processing(Attwell and Laughlin, 2001; Engl and Attwell, 2015). Despite the very high use of energy, very little energy is stored in the brain, and the neurons are thus extremely sensitive to the supply of energy(Carvalho et al., 2009). Upon circulatory arrest, brain energy stores are used up within a few minutes(Ames III, 2000); thus dE/dt rather than absolute energy stores is used in the model.

Age-induced impaired energy balance is associated with all major neurodegenerative diseases: Metabolic abnormalities feature in both PD(Dunn et al., 2014; Hipkiss, 2017; Zhang et al., 2011), AD(Hoyer, 1996; Kapogiannis and Mattson, 2011; Liang et al., 2008; Ott et al., 1996; Willette et al., 2015), and ALS(Genton et al., 2011). Diabetes and obesity are risk factors of neurodegenerative disease(Barnard et al., 2014; Kapogiannis and Mattson, 2011; Ott et al., 1996), as are genes related to cholesterol and lipoprotein homeostasis(Qiu, 2011; Toledo et al., 2012). Impaired energy availability is a key feature of these diseases(Blass, 2001; Bowling et al., 1993; Dupuis et al., 2004; Hoyer, 2000, 1996, Kepp, 2016, 2015; Liang et al., 2008; Mamelak, 2017, 2012; Rothstein, 2009) as is mitochondrial pathology(Caspersen et al., 2005; Dragicevic et al., 2010; Eckert et al., 2008; Hipkiss, 2017; Lin and Beal, 2006; Lustbader et al., 2004; Manczak et al., 2006; J. K. Morris et al., 2014; Swerdlow, 2011) Reduced energy availability in AD is well-established and sets in before clinical symptoms(Cunnane et al., 2011; De la Monte, 2014; DeToma et al., 2012; Kapogiannis and Mattson, 2011; Liang et al., 2008; Qiu, 2011; Ronnemaa et al., 2008; Zhang et al., 2015) and potential blood markers of AD relate to apoptosis and metabolism; clusterin, which is a risk factor and candidate biomarker, probably plays a central role in these pathways(Kiddle et al., 2014).

Combined Aβ and glucose exposure to microvascular endothelial cells cause enhanced cooperative chemical aging(Burdo et al., 2009). This suggests that Aβ plays a role in glucose metabolism, and Aβ can increase glucose tolerance(Marchesini et al., 1998). There is support for a direct connection between protein misfolding toxicity and accelerated aging related to disease comes from studies of Aβ effects on insulin signaling(Cohen et al., 2006). A link between proteopathy and elevated energy costs is evident from the spatial correlation between aerobic glycolysis and Aβ deposition, a relationship that may precede clinical symptoms.(Vlassenko et al., 2010) The emergence of hyperactive neurons can even precede the formation of plaques, suggesting that the pre-fibrillar soluble forms of Aβ are responsible for the hyperactive

state(Busche et al., 2012), consistent with these peptides being selectively subject to turnover costs and thus pathogenic.

PD is most likely caused by impaired ability to quality-control mitochondria of the affected cells, resulting in low energy production and associated energy shortage(Hipkiss, 2017)(Dunn et al., 2014). As is the case of AD and ALS, protein quality control is also impaired in PD(Cook et al., 2012), as is specifically the quality control of the energy-producing mitochondria, and parkin affects both mitochondrial quality control and glucose metabolism of the brain(Zhang et al., 2011).

SOD1 aggregates in sporadic ALS, and mutations cause severe early-onset familial ALS (FALS)(Dasmeh and Kepp, 2017; Kepp, 2015, 2014). ALS patients experience increased resting energy expenditure that has not been rationalized(Bouteloup et al., 2009)(Genton et al., 2011), but fits Equation (15) since SOD1 mutants almost invariably decrease stability and thus increase the pool of misfolding proteins requiring turnover. ALS-causing SOD1 mutants impair mitochondrial respiration(Mattiazzi et al., 2002; Richardson et al., 2013) and cause metabolic abnormalities(Browne et al., 2006), which supports a direct relationship between protein turnover of aggregation-prone mutants and cellular energy as quantified by Equation (15). Thus, the model suggests that ALS results from depletion of the large energy required for executing motor-neuron signaling(Dupuis et al., 2009). There is now support for this explanation(Bastow et al., 2016; Kitamura et al., 2014; Perera and Turner, 2016).

Any increased turnover of a protein also involves a cost associated with RNA processing. Some mutations do not result in amino acid changes in the produced proteins but still cause disease. The GGGGCC hexanucleotide repeat expansion on chromosome 9, C9ORF72, accounts for many cases of ALS. Such repeat expansions will lead to abnormal RNA processing and transcriptional inefficiency(Renton et al., 2011), which we argue manifest as an increased ATP cost of the cell per time unit, i.e. an increase in C_m of Equation (15). Other recently identified genetic risk factors also affect RNA metabolism (TAR-DNA binding protein 43(Sreedharan et al., 2008; Strong, 2010), FUS(Kwiatkowski et al., 2009; Vance et al., 2009)) or protein processing (SQSTM1(Fecto et al., 2011), VCP(Johnson et al., 2010)). Also, TDP-43, a risk factor in ALS, has been suggested to modulate SOD1 levels(Somalinga et al., 2012).

If the model is correct, overexpression of any protein, if substantial enough, should potentially cause energy crisis and be toxic, even if the stability and folding behavior is normal.

This has implications for many models of disease where proteins are overexpressed. Supporting this effect of the model, overexpression of non-pathogenic SOD1 wild-type proteins produce disease-like phenotypes, although these effects are smaller than for the pathogenic mutants(Jaarsma et al., 2000). These observations do not fit well with the standard models presuming an innocent wild type and a pathogenic mutant regardless of expression level, but are explained by Equation (14), where both the abundance A_i (quantitative gain of function) and the stability change (qualitative gain of function) contribute to the pool of misfolded proteins subject to turnover, and thus to the energy costs.

A simple experiment can test whether the proteomic cost minimization model or the "molecular toxic action" mechanism is most appropriate, by expressing pathogenic mutants with and without the protein being degraded. If the proteasome is inhibited during expression of the aggregation-prone mutants, disease would be aggravated if the misfolded proteins were toxic *per se*, because more toxic misfolded proteins would be available. However, if disease is mainly due to the energy burden of turnover, short-term proteasome inhibition concurrent with overexpression of pathogenic mutants should be less pathogenic than the same mutants expressed at the same levels without proteasome inhibition on a short time scale until the inhibition of protein turnover becomes systemically toxic. An experiment support this prediction of the model was done with the pathogenic G85R mutant of SOD1, which was not very toxic during inhibition of the proteasome, but became so when the proteasome activity was recovered after inhibition(Kitamura et al., 2014). The general assumption that a molecular mode of action makes misfolded proteins toxic is not supported by such experiments. Equation (14) explains it because the toxic mode of action is not in the misfolded protein copy itself, but in its associated turnover cost.

There is substantial evidence that caloric restriction improves memory and postpones neurodegeneration in some people(Halagappa et al., 2007; Luchsinger et al., 2002; Witte et al., 2009). According to the free radical theory of aging(Harman, 2003; Speakman et al., 2002), lower mass-specific metabolic rates (as seen in larger animals) lead to longer lifespan, possibly because of reduced mass-specific free radical production per time unit. Extended life span is also seen upon caloric restriction in animals.(Colman et al., 2014; Madeo et al., 2014; Shanley and Kirkwood, 2000) Since the main risk factor of AD is age, a lower mass-specific metabolic rate could be a confounding variable of AD risk, by simply decelerating aging, but it could also directly relate to metabolic efficiency. Caloric restriction reduces the specific metabolic rate,

which is likely to reduce oxidative insults to the energy balance, but more importantly improves the efficiency of mitochondria by active selection pressure, at the center of the energy balance (**Figure 1**).(Civitarese et al., 2007; Lopez-Lluch et al., 2006)

6. Concluding remarks

There is a pressing need for new fundamental understandings of neurodegenerative diseases and for models that can combine and rationalize the vast amount of data in the field. This paper provides such a model relating protein turnover directly to clinical outcome via an energy balance equation. The principle of proteome cost minimization holds that neurons are among the most energy-demanding cells in the body, that the cost of protein turnover reduces the energy left for ion pumping and thus cell signaling, and that the age-induced increased energy costs and reduced energy production produce a threshold where energy available for cognitive execution becomes critical, the age of symptom onset. Abundant, aggregation-prone proteins will increase maintenance cost and thus accelerate aging. Turning on and off the proteasome by inhibitors during pathogenic mutant expression in cultured cells should be a straightforward way to test the theory. The model also provides an alternative, systemic explanation for the sigmoidal shape of biomarkers not due to aggregation kinetics of proteins but to accelerating energy costs of the cells due to a variety of mechanisms.

The equations suggests multiple strategies to address the diseases, notably by either increasing total energy availability, energy efficiency, or by reducing maintenance costs. Therapies that target those oligomers that are particularly subject to proteolysis *in vivo* are predicted to be most advantageous. The predictions are in contrast to those of the traditional view that protein aggregates have a specific toxic mode of action that should be targeted, and that any turnover of them, however costly, should be less important to disease course. Such clinical strategies have so far failed perhaps for the reasons stated in this work. Instead, the increasing evidence for the case of targeting energy balance in neurodegenerative diseases (Gejl et al., 2016) is supported by the model described in the present work. Another strategy is to strengthen the mitochondrial efficiency by e.g. controlled caloric restriction, which could improve the energy balance by increasing selection pressure on mitochondrial efficiency before disease onset.

Conflicts of interest

The author declares that he has no financial or non-financial interests associated with this work.

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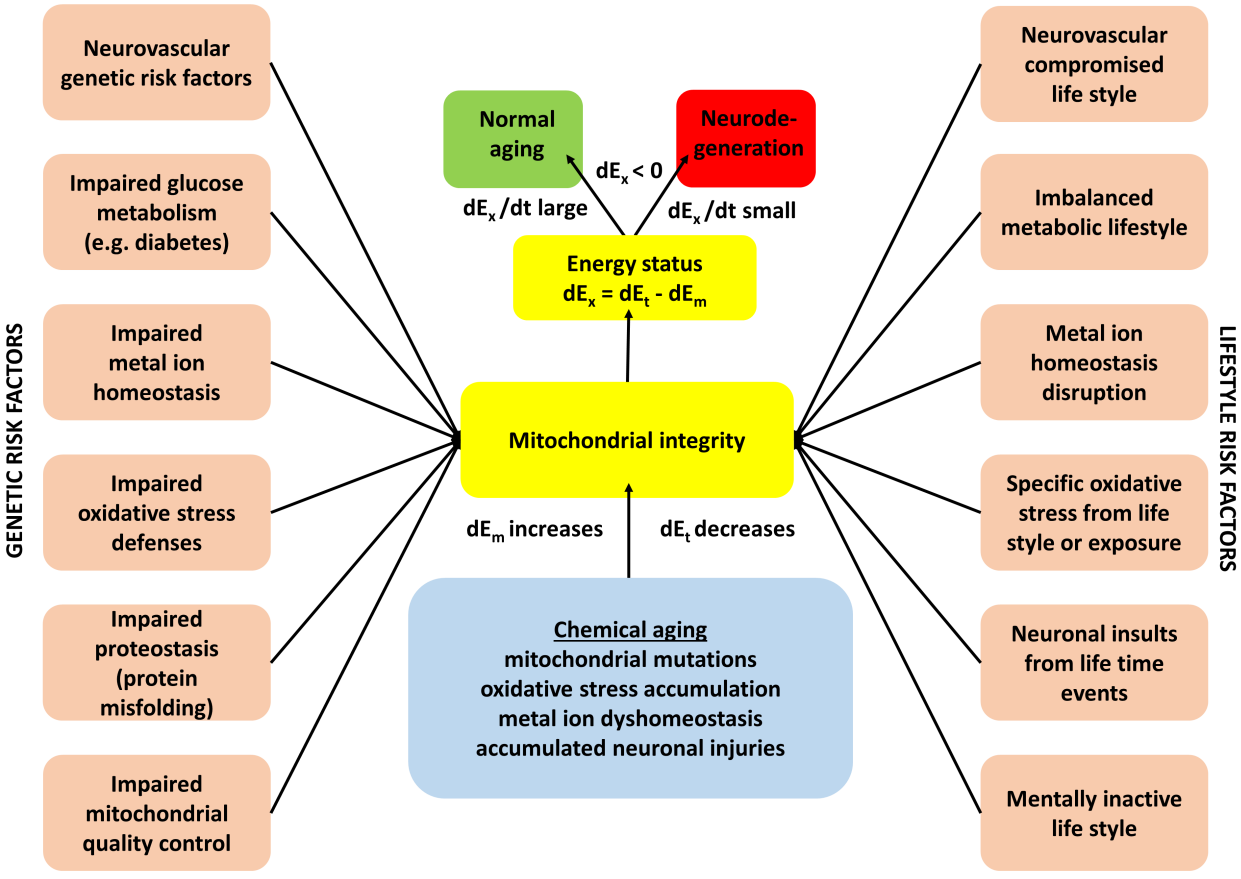
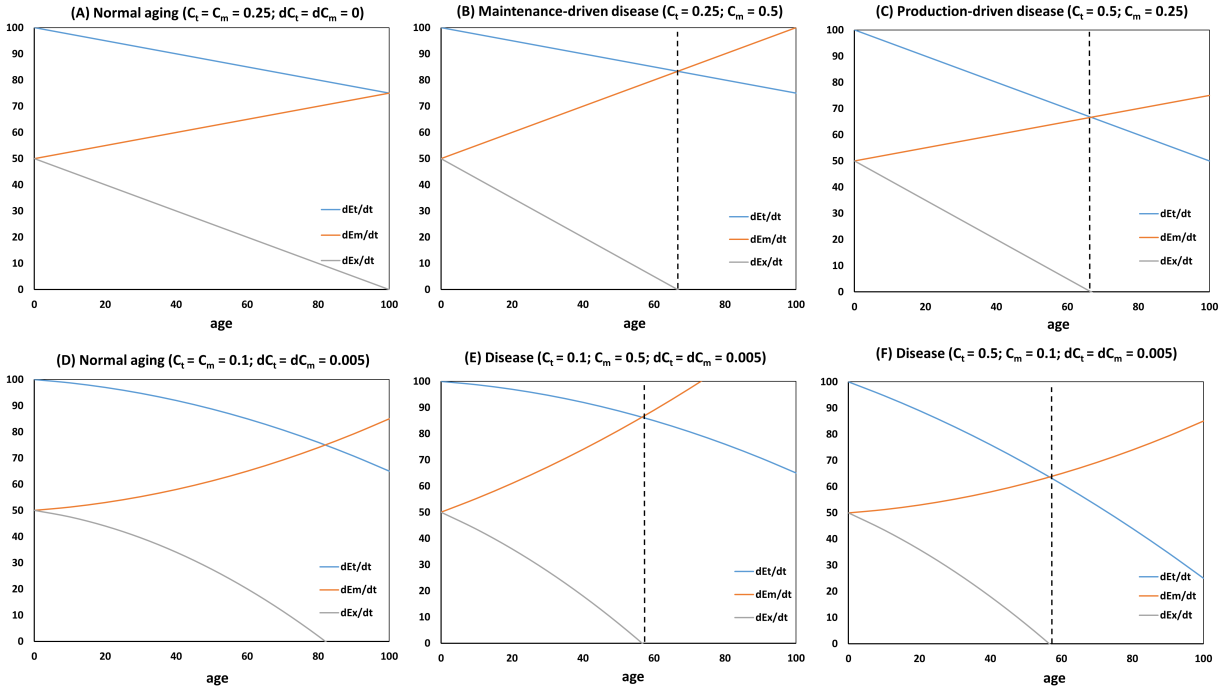
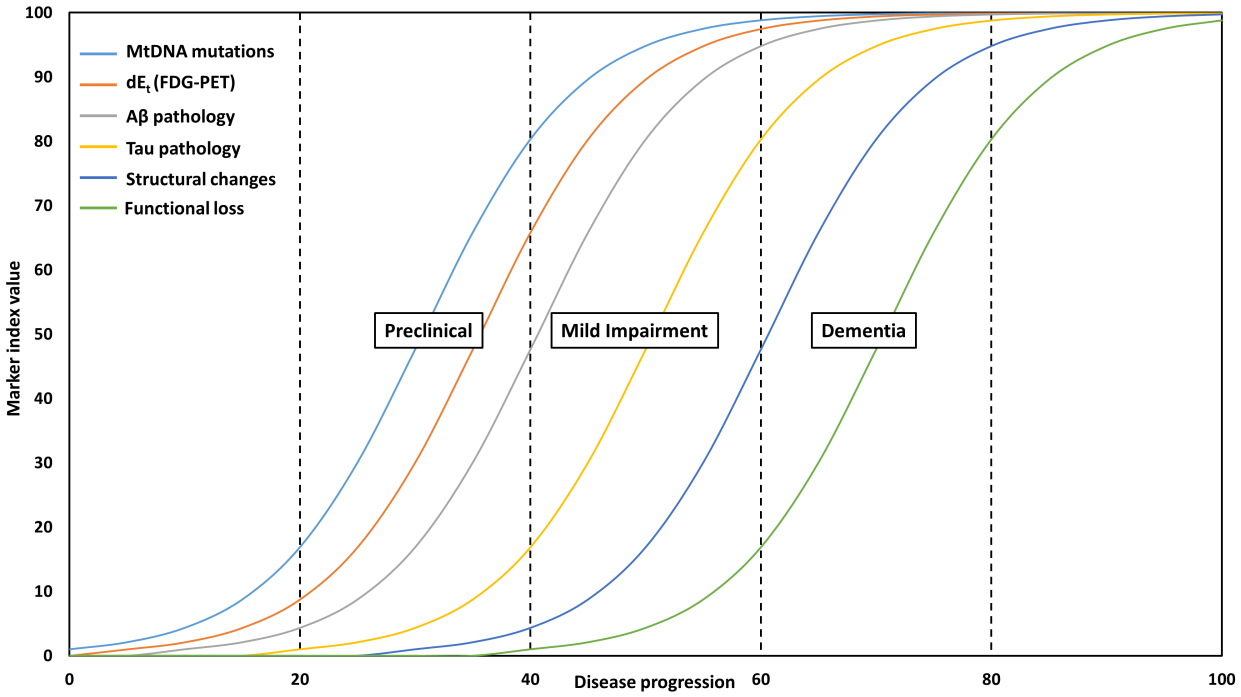

GENETIC RISK FACTORS
Neurovascular genetic risk factors
Impaired glucose metabolism (e.g. diabetes)
Impaired metal ion homeostasis
Impaired oxidative stress defenses
Impaired proteostasis (protein misfolding)
Impaired mitochondrial quality control
Normal aging
Neurode-generation
$dE_x < 0$
dE_x/dt large
dE_x/dt small
Energy status
$dE_x = dE_t - dE_m$
Mitochondrial integrity
dE_m increases
dE_t decreases
Chemical aging
mitochondrial mutations
oxidative stress accumulation
metal ion dyshomeostasis
accumulated neuronal injuries
Neurovascular compromised life style
Imbalanced metabolic lifestyle
Metal ion homeostasis disruption
Specific oxidative stress from life style or exposure
Neuronal insults from life time events
Mentally inactive life style
LIFESTYLE RISK FACTORS





- Human neurodegenerative diseases involve protein aggregation
- The computational model explains how protein misfolding cause disease
- It uses proteomic energy cost minimization as its core principle
- Disease onset occurs when all energy is spend on protein maintenance
- The model rationalizes the sigmoidal shape of biomarker histories