Working With Convex Responses: Antifragility From Finance to Oncology

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Abstract—We extend techniques and learnings about the stochastic properties of nonlinear responses from finance to medicine, particularly oncology where it can inform dosing and intervention. We define antifragility. We propose uses of risk analysis to medical problems, through the properties of nonlinear responses (convex or concave). We 1) link the convexity/concavity of the dose-response function to the statistical properties of the results; 2) define "antifragility" as a mathematical property for local beneficial convex responses and the generalization of "fragility" as its opposite, locally concave in the tails of the statistical distribution; 3) propose mathematically tractable relations between dosage, severity of conditions, and iatrogenics. In short we propose a framework to integrate the necessary consequences of nonlinearities in evidence-based oncology and more general clinical risk management.
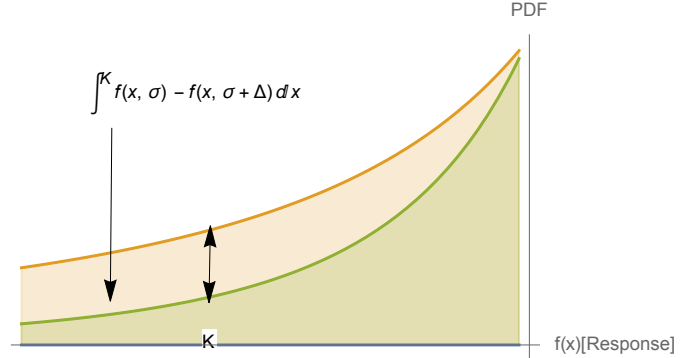
I. Introduction: Where the Idea of Antifragility Came From

The notions of fragility and antifragility were inspired from the payoffs and the intricacies of financial derivatives. The concept was introduced in Taleb (2012) [17] and more formalized in Taleb and Douady (2013) [68]. While in the real world many phenomena are intuitively known to benefit from an increase in "volatility"[1], only quantitative finance had names for such attributes, such as "long gamma"[2], "long vega"[3], and similar measures, always associated with some range of variation as these sensitivities are local and have themselves higher derivatives. Furthermore finance links some nonlinear attributes of portfolios to the risk of "blowups" that is, a loss large enough to be irreversible, that is, irrecoverable financial ruin. Such quantitative and qualitative models of ruin can give us a tractable generalizable definition of fragility. But centrally, Derivatives risk management, at its core, lies in distinguishing between the properties of a random variable X and a payoff function $f(x)$, almost always nonlinear.

While Jensen's inequality (on which more in A) is concerned with the first moment of the distribution, monotone convex (or concave) functions, and with a static expectation operator, financial payoffs are more complicated: the first static moment, while relevant, is not the sole focus as:

[1]Usually and unless otherwise specified, the term *volatility* maps to the standard deviation of the random variable, or the variability of a nonrandom one.

[2]The financial "derivative" contract has a positive local second mathematical derivative with respect to the underlying security.

[3]The financial derivative has a positive first derivative with respect to the standard deviation of the underlying security (or the returns of the security).

Fig. 1. Fragility below level K as indicative of survival. It is not quite symmetric because global antifragility is conditioned on tail robustness ("to do well one must first survive"). The Taleb and Douady (2013)[68] paper shows that the gap between $\int^K f(x,\sigma)dx$ and $\int^K f(x,\sigma+\Delta)dx$ where σ is the scale of the distribution is proportional to the concavity of $f(x)$. Hence without knowing the distribution (PDF above), one can gauge such effect by looking at the nonlinearity of $f(.)$ below the threshold K.

- The expectation must be conditioned on absence of "blowup", that is the left tail of the distribution must be constrained (see Geman et al, 2015)[103], which involves all higher moments of $f(x)$.
- The payoff functions are almost never monotone.
- Taking into account higher moments of the distributions is analog to going beyond second order effects: third, fourth, etc.

Fragility: fragility as defined is related to how a system suffers from the variability of its environment beyond a certain preset threshold (when the threshold is K, it is called K-fragility), see Figure 1, while antifragility refers to when it benefits from this variability —in a similar way to as we saw what quantitative finance calls "vega" for an option or a nonlinear payoff, that is, its sensitivity to volatility or some similar measure of scale of a distribution. (Tail fragility maps to a risk of financial ruin, while local fragility does not necessarily mean ruin). In Taleb and Douady (2013)[68]:

> *Simply, a coffee cup on a table suffers more from large deviations than from the cumulative effect of some shocks—conditional on being unbroken, it has to suffer more from "tail" events than regular ones around the center of the distribution, the 'at-*

the-money' category. This is the case of elements of nature that have survived: conditional on being in existence, then the class of events around the mean should matter considerably less than tail events, particularly when the probabilities decline faster than the inverse of the harm, which is the case of all used monomodal probability distributions. Further, what has exposure to tail events suffers from uncertainty; typically, when systems—a building, a bridge, a nuclear plant, an airplane, or a bank balance sheet—are made robust to a certain level of variability and stress but may fail or collapse if this level is exceeded, then they are particularly fragile to uncertainty about the distribution of the stressor, hence to model error, as this uncertainty increases the probability of dipping below the robustness level, bringing a higher probability of collapse. In the opposite case, the natural selection of an evolutionary process is particularly antifragile, indeed a more volatile environment increases the relative survival rate of robust species and eliminates those whose superiority over other species is highly dependent on environmental parameters.
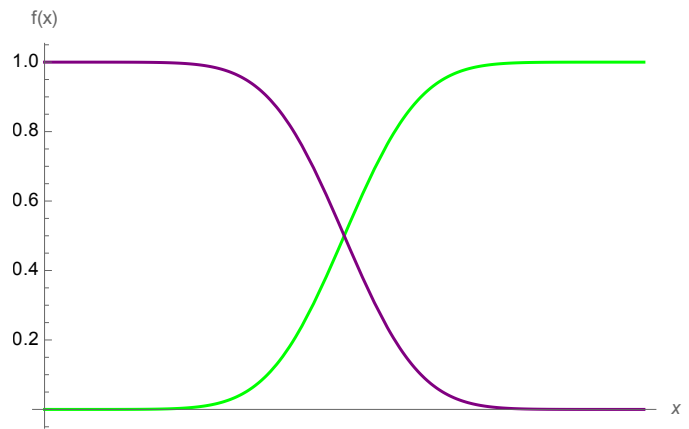

Fig. 2. Simple (first order) nonincreasing or nondecreasing sigmoids, defined as floored and capped increasing functions. They map to the payoff in finance of a binary option with time left to expiration. As the sigmoid loses in smoothness (with the decrease time to expiration), it becomes at the limit a Heaviside function, see Fig.3.
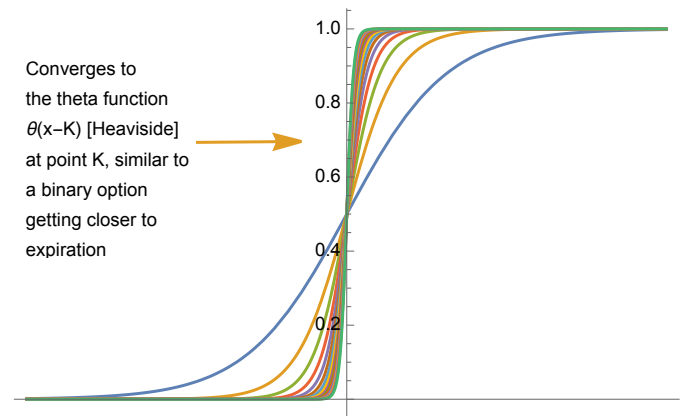

Fig. 3. The smoothing of the Heaviside function as distribution or Schwartz function.

The paper above produced theorems linking the second derivative of $f(x)$ in some ranges of variation to sensitivity to the scale of the distribution of X. Thus the same sensitivity to the scale of the distribution can also express sensitivity to a stressor (dose increase) in medicine or other fields in its effect on either tail. Thus one single measure will allow us to express with comfortable precision the exposure to the *disorder cluster*: (i) uncertainty, (ii) variability, (iii) imperfect, incomplete knowledge, (iv) chance, (v) chaos, (vi) volatility, (vii) disorder, (viii) entropy, (ix) time, (x) the unknown, (xi) randomness, (xii) turmoil, (xiii) stressor, (xiv) error, (xv) dispersion of outcomes. Finally –and critically –the paper showed that one does not need to have an exact probability distribution to get a useful idea of the exposure since these metrics are based on acceleration, which washes out up to one order of magnitude the precision errors[4].

Asymmetry Fragile/Antifragile: The opposite of globaly fragile (with respect to a random variable X) is not naively "antifragile", but both convex with respect to that variable and have a left tail constraint. In probabilistic representation $f(x)$ must have a positively skewed distribution.

The rest of this article will present medicine and convexity, then apply the notions of fragility-antifragility at two level: efficient dosing in oncology and an examination of iatrogenics as linked to convexity[5]. Finally we present in the appendix an overview of convex responses in medicine.

II. MEDICINE AND CONVEXITY

Medicine has much simpler payoffs than quantitative finance. Most are generalizations around simple sigmoids, see Fig. 2, which were described in the mapping in Taleb and Douady (2013)[68] as belonging to the benign class: the distribution of $f(x)$ is necessarily thinner tailed than that of X owing to the boundedness of the function, dubbed more "binary" than "vanilla", see [104].

However, in spite of such simplicity, little work in medicine has been done about probabilistic effect on convexity –almost always limited to first order effects and comparative statics. The probabilistic dimension of variability has been made

[4]For multivariate situations, an additive approach is used without any loss of effectiveness.

[5]We use by convention the term "convexity" or "convexity effect" in the presence of consequential nonlinearity, which can be concave: if the harm function is defined as positive it shows as convex, if negative, it shows as concave. Finance uses the expression "convexity bias" for both concave and convex responses (and with possible additional designation "positive" or "negative" convexity).

explicitly in some medical domains, for instance there are a few studies connecting Jensen's inequality to patient responses with pulmonary ventilators: papers such as Brewster et al. (2005)[1], Amato et al. [5], Funk (2004)[3], Arold et al. (2003)[4], Graham et al.(2005) [2], Mutch et al. (2007). To summarize the literature, continuous high pressures have been shown to be harmful (leading to increased mortality), but episodic spikes of ventilation pressures can be helpful with the recruitment of collapsed alveoli. However these papers stop at Jensen's inequality, and, further, explicit probabilistic formulations are still missing in other domains where the applications of these techniques are most needed, such as intermittent fasting, episodic energy deficit, uneven distribution of sub-groups (say, proteins), vitamin absorption, moderate and low intensity training, fractional dosage, the comparative effects of low-intensity and distributed intervention vs intense and concentrated ones, the chronic vs the acute, and similar effects. The identification of convexity is still confined to local responses and did not generalize to decision-making under uncertainty and inferences concerning silent risks from the nonlinearity in dose-response. For instance the results did not reach the obvious relation between tumor size and the trade-offs of the intervention, or the extrapolation between the numbers needed to treat (NNT) and the potential severity of the side effects.

The connections we are investigating are necessary and mathematical: they work in both directions. We can illustrate as follows:

- a convex response to energy balance over a fixed time window necessarily implies gains from intermittent fasting (that is, higher variance in the distribution of nutrients) over some range within the limits of that time window,
- the presence of metabolic problems in populations that have a steady supply of food intake, as well as evidence of human fitness to an environment that provides moderate variations in the availability of food, both necessarily imply a concave response to food within a range and time frame.

Finally, a short summary of the above is as follows. Convexity analysis in medicine is at two dimensions, first, working with the nonlinearity of dosing, second, for risk analysis for patients and groups.

Missing second order effect: One frequent lacuna in the literature is ignoring the second order effects when making statements derived from from empirical data. One example is dietary recommendations for food group composition rather than frequency. Epidemiological interpretations of the Cretan diet relied solely on composition. But frequency matters: the Eastern Orthodox Church has, with minor local variations, around two hundred days of vegan fasts per year. This is an episodic protein deprivation; fatty meats are consumed in lumps (on Sundays and holidays) which compensate for such a deprivation (recall the threshold in Fig.5. As shown in the literature review in Appendix A, there is a need for a mathematical bridge between studies of *variability*, say Martin et al.(2006) [27] and Fontana et al (2008)[105] on one hand,

and the focus on *composition* –the Longo and Fontana studies, furthermore, narrows the effect of the frequency to a given food type, namely proteins[6]. Further, the computation of the "recommended daily" units may vary markedly if one assumes necessary stochasticity.

Extracting past statistical attributes and frequencies: A central question is that if we need a certain dose of stressors, whether in intermittence of nutrition or necessary exercise, these might represent the attributes of an "ideal" environment. Whether evolutionary or not, this is the one to which we are most adapted stochastically. We can therefore reverse engineer the stochastic nature of such an "ideal" environment by finding the various conditions that result from reduction of stressors. We noted that papers such as Kaiser (2003) [21] and Calabrese and Baldwin (2003), [24] do not bridge the results to the point that hormesis may correspond to a "fitness dose", beyond and below which one departs from such ideal dispersion of the dose x per time period.

Such a reverse engineering uses the visible dose-response curve to make inferences about the ideal parametrization of the probability distribution of nutritional balance and vice-versa. For example, assessing the benefits of episodic fasting and the length of windows for neoplasms, insulin resistance, and other conditions can lead to understanding some kind of "fitness" to an environment endowed with a certain structure of randomness, either with the σ above or some more sophisticated attributes of the probability distributions. For example, if insulin resistance can be reduced thanks to occasional deprivation (a certain variance), say one 24 hour fast every week, 3 days of fasting per trimester, and a complete week every five years, then we can extract and parametrize a probability distribution of ancestral deprivations. A comprehension of the exact mechanism by which such intermittences works can be helpful but is not needed given the robustness of the mathematical connection between functional and probabilistic.

A. Antifragility in treatment scheduling

In figure 4, the input distribution of dose x is subject to the convexity (or concavity or linearity) of the dose response function, which influences the tail of the outcome distribution. Importantly, an oncologist has "first-mover" advantage [7] and has the benefit of prescribing an "even" treatment protocol with no variance (figure 5, top row) or an "uneven" treatment protocol with positive variance (figure 5, bottom row).

In medical practice, treatment protocols are typically fixed with doses administered at regular intervals (e.g. figure 5). The distribution of dosing is unimodal (purple; continuous dosing), or at most bimodal (green; intermittent dosing). Manipulation of dose volatility when designing treatment protocols is underutilized as a strategy in cancer treatment. In place of a dose x, one can give, say, 120% of x, then 80% of x, with a more favorable outcome one is in a zone that benefits from unevenness. If antifragile, more unevenness is more beneficial: 140% followed by 60% produces better effects [107].

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[6]Lee and Longo (2011) [19] "In the prokaryote E. coli, lack of glucose or nitrogen (comparable to protein restriction in mammals) increase resistance to high levels of H_2O_2 (15 mm) (Jenkins et al., 1988) [20]"
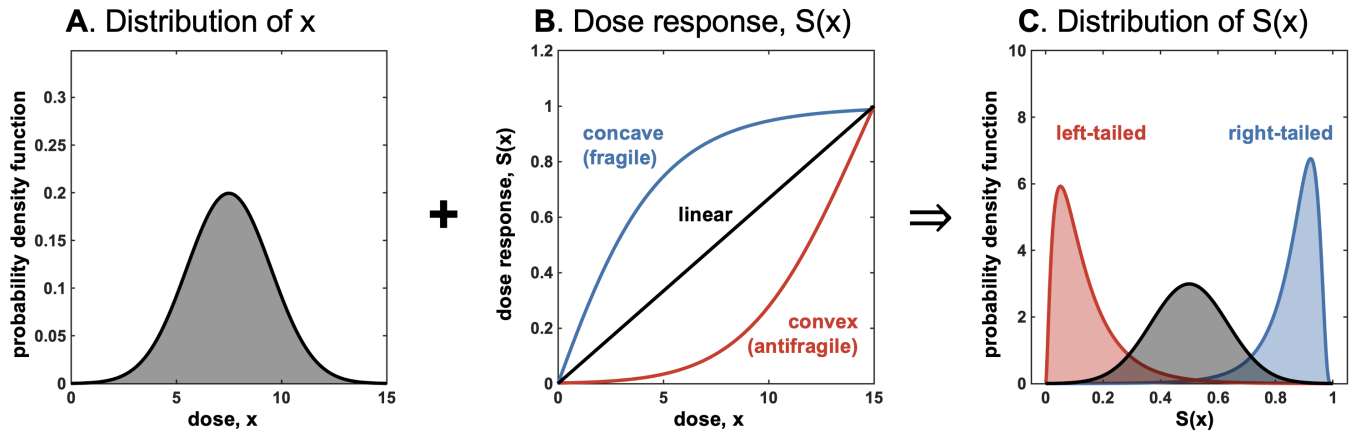
Fig. 4. These two graphs summarize and simplify our main idea: how we can go from the reaction or dose-response $S(x)$, combined with the probability distribution of x, to the probability distribution of $S(x)$ and its properties: mean, expected benefits or harm, variance of $S(x)$. Thus we can play with the various parameters that can affect $S(x)$ and those that can affect the distribution of x, and extract results from the output. $S(x)$ as we show can take different forms (We chose a monotone convex or concave $S(x)$ but can also use a second order mixed sigmoid).
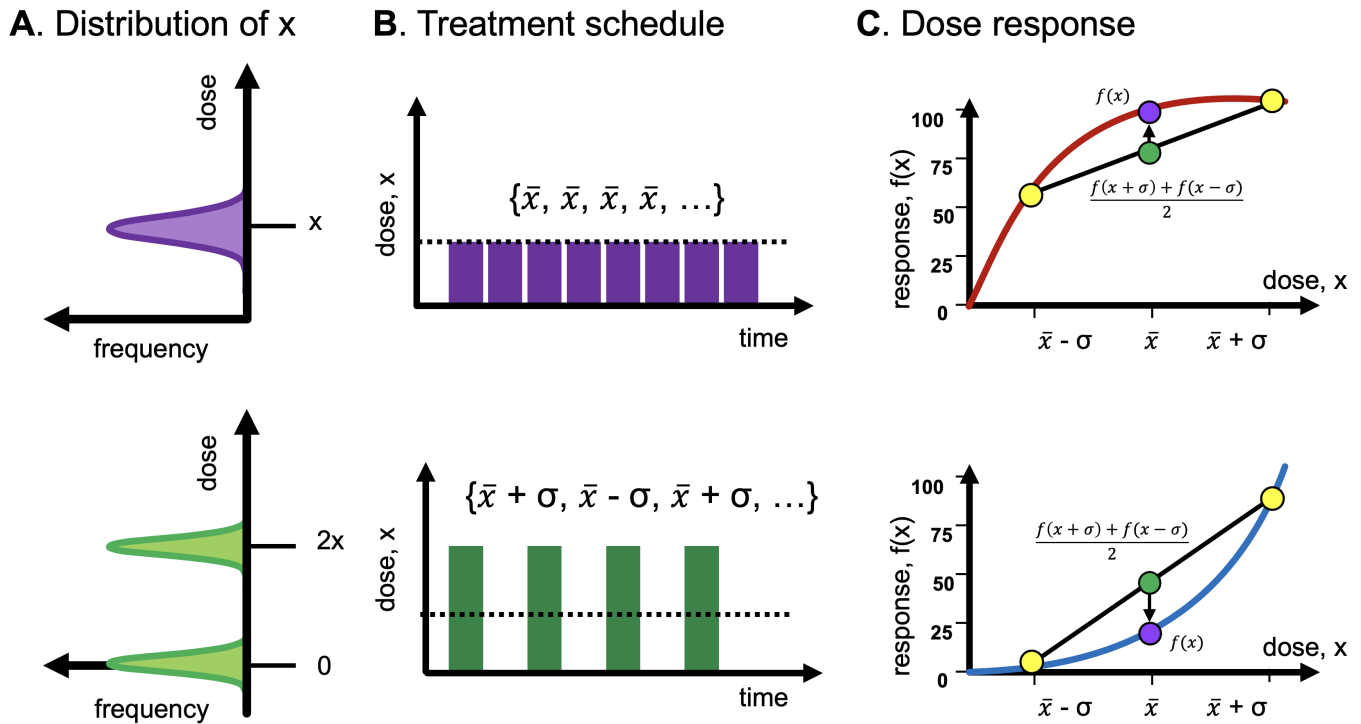

Fig. 5. Example treatment scheduling protocols. (A) Input distribution of dosing is typically unimodal ("even") or bimodal ("uneven"). (B) Protocols are typically fixed, with doses administered at regular intervals. It may be feasible to temporarily increase the dose (green), with periodic treatment holidays. (C) Even treatment is optimal to maximize response for concavity; uneven for convexity.

III. ANTIFRAGILITY IN ONCOLOGY

Across all treatment modalities, cancer treatment is intended to induce perturbations to environmental conditions within a tumor leading to cell death, altering vasculature, or impacting immune response. However, the most common treatment paradigm is the "maximum-tolerable dose" (MTD) dosing protocol, whereby the dose is maximized, and only limited by tolerability, toxicity, and side-effects. To re-phrase, oncology research is implicitly focused maximizing "first-order" treatment effects by increasing the cumulative dose. The "log-kill" law proposes an MTD protocol for cytotoxic chemotherapy agents that decreases the amount of time over which a cumulative dose is delivered as toxicity allows[8]. More recently, metronomic therapy proposes frequent, low doses known to provide an anti-angiogenic effect during chemotherapy – still implicitly optimizing a first-order effect of cumulative dose: [9].

Oncology must consider convexity in strategizing treatment protocols. Although convexity was not a consideration initial clinical design, recent approaches have had success in managing second-order effects through the practice of high / low dosing. Intermittent high dosing of tyrosine kinase inhibitors (TKI) in HER2-driven breast cancers was administered with concentrations of the drugs that would otherwise far exceed toxicity thresholds if dosed continuously [10]. Continuous letrozole in combination with high dose intermittent ribociclib is currently in clinical trial (NCT02712723; ER-positive breast cancer) [11]. Intermittent high dose erlotinib delays resistance in an EGFR-mutant non–small cell lung cancer in vivo model [12], [13]. Intermittent weekly EGFR-inhibitors reduced tumor load in vivo, compared with daily regimens with identical cumulative dose [14]. Intermittent "pulsatile" high dose erlotinib once weekly maintains efficacy even after failure low dose continuous [15]. Ideal treatment protocols will maximize both first-order effects (cumulative dose) in addition to second-order effects (variance of dose delivered). Studies mentioned previously provide evidence of the tolerability of temporary dose escalation by also employing off-treatment periods to alleviate therapy toxicity.

A. Defining (local) fragility in oncology

Local Fragility, F, is a measurable quantity, similar to the Jensen Gap, defined as the difference in result of unevenness over evenness (with corresponding unevenness range parameter λ):

$$F(x, \lambda) = \frac{f(x + \lambda) + f(x - \lambda)}{2} - f(x) \qquad (1)$$

What property of cancer cells, $f(x)$, is important in oncology? Here, we are interested in the gain of "uneven" high / low schedule over the "even" schedule. More precisely, fragility is the difference between 1) a schedule of two constant doses (termed an "even" dosing strategy), $\vec{X} = \{x, x\}$ and 2) a schedule of a high dose followed by a low dose (termed an "uneven" dosing strategy), $\vec{X} = \{x + \lambda, x - \lambda\}$. We consider the response to two doses over an interval of time T, where the first dose is given at $t = 0$ and the second dose is given

at $t = T/2$. Given a tumor with initial population size of n_0, the final size of an exponentially-growing population is given by:

$$n_F(t) = n_0 \exp(\gamma(x)t), \qquad (2)$$

where $\gamma(x)$ is the decay rate of the population associated with a dose of x. Fragility can be defined as:

$$F(x, \lambda) = n_0 \exp\left(\gamma(x+\lambda)\frac{T}{2}\right) \exp\left(\gamma(x-\lambda)\frac{T}{2}\right) - n_0 \exp\left(\gamma(x)\frac{T}{2}\right) \epsilon \qquad (3)$$

which simplifies to:

$$F(x, \lambda) = n_0 \left[\exp\left((\gamma(x+\lambda) + \gamma(x-\lambda))\frac{T}{2} \right) - \exp\left(\gamma(x)T\right) \right]. \qquad (4)$$

We are interested in the antifragile-fragile boundary, the point at which the population is no longer fragile but antifragile:

$$F(x, \lambda) = \frac{\gamma(x+\lambda) + \gamma(x-\lambda)}{2} - \gamma(x) \qquad (5)$$

If $F < 0$, the cell population is antifragile by definition (a benefit conferred to uneven dosing for minimizing tumor growth rate) and if $F > 0$, then fragile. Thus, the important domain for convexity is the dose-dependent growth rate, $\gamma(x)$. It is an unfortunate common practice to normalize dose response curves to obtain fractional survival at the final time point (e.g. $1 - n_F/n_0$), which obscures convexity. Drug-induced growth rate inhibition (GR curves) have been introduced as a method to remove the artifactual dependency of IC50 and Emax on cellular division rate[16]. GR-curves preserve convexity, unlike fractional survival.

B. Fragility and Taylor Series Approximations

Antifragility is a "second-order" effect. This is shown by first taking a Taylor Expansion about x:

$$f(x \pm \lambda) = f(x) \pm \lambda f'(x) + \frac{\lambda^2}{2} f''(x) + O(\lambda^3) \qquad (6)$$

where $O(\lambda^3)$ represents all third-order or higher terms. Using this expansion, fragility can be written:

$$F(x, \lambda) = \frac{1}{2}\left(2f(x) - f(x) - \lambda f'(x) - \frac{\lambda^2}{2} f''(x) - f(x) + \lambda f'(x) - \frac{\lambda^2}{2} f''(x) \right) \qquad (7)$$

The zeroth-order terms and the first-order terms cancel out:

$$F(x, \lambda) = -\frac{\lambda^2}{2} f''(x) + O(\lambda^3) \qquad (8)$$

For small values of λ, fragility is proportional to the second derivative, and thus known as a second-order effect. Next, we connect the concept to finite difference methods.

C. Fragility and finite differences

We can approximate the derivative of $f(x)$ using finite differences. Here, we use central finite differences to obtain:

$$\frac{\Delta f}{\Delta x} = \frac{f\left(x + \frac{h}{2}\right) - f\left(x - \frac{h}{2}\right)}{h}. \qquad (9)$$

This difference quotient is a first-order approximation of $f'(x)$ where h is the width of the interval over which the finite

difference is estimated ($h > 0$). The approximation error is proportional to h. Taking the limit as $h \to 0$ allows us to express $f'(x)$ in terms of this approximation:

$$f'(x) = \lim_{h \to 0} \frac{f\left(x + \frac{h}{2}\right) - f\left(x - \frac{h}{2}\right)}{h}. \quad (10)$$

By iterating the central finite differences process once more, we can derive the finite difference quotient for $f'(x)$:

$$\frac{\Delta f'}{\Delta x} = \frac{f(x+h) - 2f(x) + f(x-h)}{h^2}. \quad (11)$$

This difference quotient provides an approximation $f''(x)$ with an error proportional to h^2. Taking the limit as $h \to 0$ yields the second derivative of $f(x)$:

$$f''(x) = \lim_{h \to 0} \frac{1}{h^2}[f(x+h) + f(x-h) - 2f(x)]. \quad (12)$$

The term on the right-hand side in brackets is related to fragility (eqn. 1), giving us the relationship between $F(x, \lambda = h)$ and $f''(x)$:

$$f''(x) = -\lim_{h \to 0} \frac{2}{h^2} F(x, h), \quad (13)$$

This limit illustrates that $f''(x)$ approaches F only when h is small. When the value of h is large, the approximation is poor, and therefore we employ equation 1. Figure 6 provides an example of approximation error for the Hill function (see next section).

D. Applications to Hill function

The Hill function is commonly used to describe the drug pharmacodynamics[106], where $H(x)$ is the cell viability in response to a dose x.

$$H(x) = \frac{E_1 - E_0}{1 + \left(\frac{C}{x}\right)^n} + E_0 \quad (14)$$

where n is the Hill shape parameter, E_0 and E_1 are the minimal and maximal response (respectively), and C is the half-maximal response (the EC50 value). The second derivative can be written:

$$\frac{d^2 H}{dx^2} = \frac{(E_1 - E_0)nC^n x^{n-2}((n-1)C^n - (n+1)x^n)}{(C^n + x^n)^3}. \quad (15)$$

Figure 6A shows a sample Hill function and corresponding second derivative. Figure 6B illustrates decreasing error between the numerical (F) and analytical ($\frac{d^2 H}{dx^2}$) as $h \to 0$. The error scales like h^2, as predicted in equation 13. The inflection point, found where $\frac{d^2 H}{dx^2} = 0$, defines the boundary between convex and concave regions.

$$x^* = C\left(\frac{n-1}{n+1}\right)^{1/n} \quad (16)$$

It can be shown that as n increases, $x^* \to C$. Importantly, x^* determines the boundary between antifragile and fragile regions of $f(x)$. Benefit can thus be derived from uneven dosing if $x < x^*$. The converse implies that uneven treatment schedules provide no additional benefit.

We can relax the assumption of fixed treatment schedules (e.g. figure 5). Given some input probability density function describing the distribution of dose, $p(x)$, the probability density can be determined for the Hill function analytically. Let X (dose concentration) and $Y = H(X)$ be random variables. The probability density function transformation, $P(y(a) \le Y < y(b))$, is given by:

$$P = \int_a^b p(x)dx = \int_{y(a)}^{f(b)} p(x(y))\left|\frac{dx}{dy}\right|dy \quad (17)$$

$$P = \int_a^b p\left(C\left(\frac{E_1 - E_0}{y - E_0}\right)^{\frac{-1}{n}}\right)$$
$$\left|\frac{C(E_1 - E_0)}{n(E_0 - y)^2}\left(\left(\frac{E_0 - E_1}{E_0 - y}\right) - 1\right)^{\frac{-(n+1)}{n}}\right|dy \quad (18)$$

As shown in figure 4, the input distribution passing through convex dose response (e.g. on the Hill function below its inflection point) result in a left-tailed outcome distribution, and a concave response function results in a right-tailed distribution.

Thus, we have defined as locally antifragile a situation in which, over a specific interval $[a, b]$, either the expectation rises with the scale parameter of the probability distribution as in Eq. 22, or the dose response is convex (on average) over the same range. The designation in Taleb (2012) [17] meant to accurately describe such situations: anything that gains from an increase in stochasticity or variability (since the scale parameter represents both). Terms like "resilience", since they were not mapped mathematically, are vague and even confusing as they meant either resistance or gains from stressors, depending on context. Fig. 7 and 8 illustrates the threshold effect of the asymmetric response, and gives the intuition of how they can be described as as antifragile.

E. The first order sigmoid curve

Next we outline the variety of sigmoids as catalogued by [101]. Define the sigmoid or sigmoidal function as having membership in a class of function $\mathfrak{S}$, $S : \mathbb{R} \to [L, H]$, with additional membership in the $\mathbb{C}^2$ class (twice differentiable), monotonic nonincreasing or nondecreasing, that is let $S'(x)$ be the first derivative with respect to x: $S'(x) \ge 0$ for all x or $S'(x) \le 0$. We have:

$$S(x) = \begin{cases} H & \text{as } x \to +\infty; \\ L & \text{if } x \to -\infty. \end{cases},$$

which can of course be normalized with $H = 1$ and $L = 0$ if S is increasing, or vice versa, or alternatively $H = 0$ and $L = -1$ if S is increasing. We can define the simple (or first order) sigmoid curve as having equal convexity in one portion and concavity in another: $\exists k > 0$ s.t. $\forall x_1 < k$ and $x_2 > k$, $\text{sgn}(S''(x_1)) = -\text{sgn}(S''(x_2))$ if $|S''(x_2)| \ge 0$.

Now all functions starting at 0 will have three possible properties at inception, as in Fig. 10: concave, linear, convex. The point of our discussion is the latter becomes sigmoid and is of interest to us. Although few medical examples
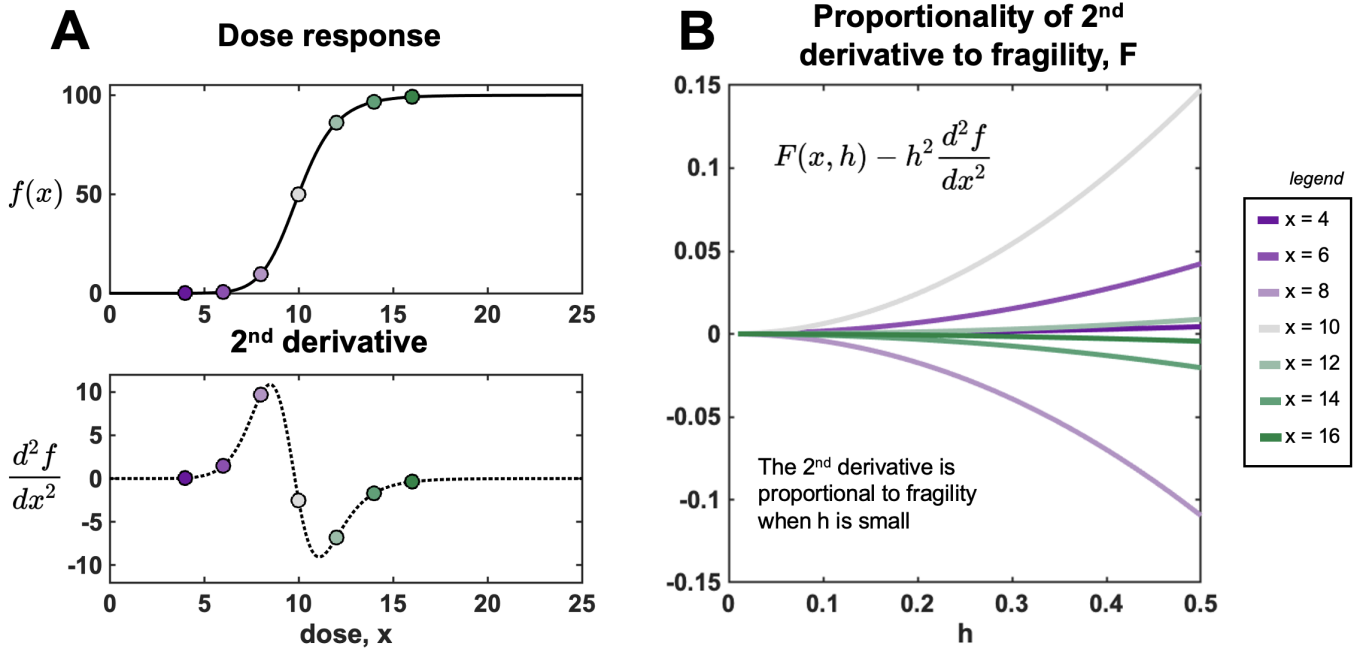
Fig. 6. **The second-derivative is an approximation for fragility for low values of h.** (A) Hill function, $H(x)$ (eqn. 14) shown for $n = 10$, $E_0 = 0$, $E_1 = 100$, $C = 10$. Analytically derived second-derivative (eqn. 15) is shown in the bottom panel. (B) Difference between fragility and second-derivative at various dose values (red to blue) corresponding to panel A. As $h \to 0$, the error approaches zero: $F(x, h) - h^2 \frac{d^2 H}{dx^2} \to 0$.
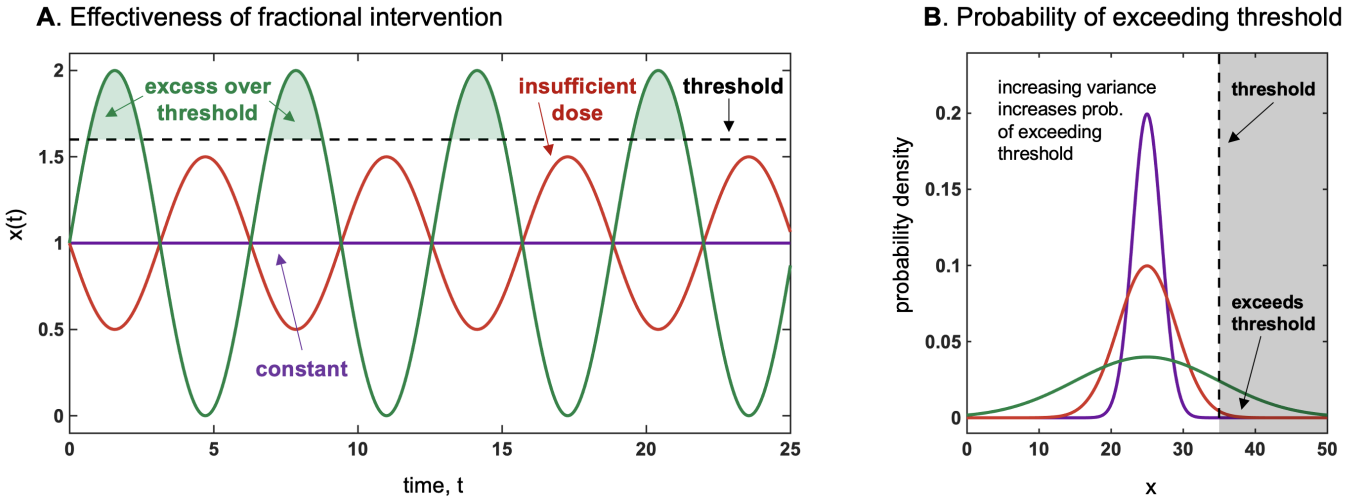

Fig. 7. (A) How a fractional intervention is more effective to surpass a threshold than a constant dosage of the same average. This is akin to **stochastic resonance** (in physics) by which the presence of noise cause the signal to rise above the detection threshold. For instance, genetically modified BT crops produce a constant level of pesticide, which appears to be much less effective than occasional manual interventions to add doses to conventional plants. The same may apply to antibiotics, chemotherapy and radiation therapy. (B) How more variance impacts the exceedance over the threshold. If threshold $\geq$ mean, we have convexity and the variance increases the payoff more than variations in the mean. Such an effect is proportional to the remoteness of such threshold. Note that the harm function is defined as positive.
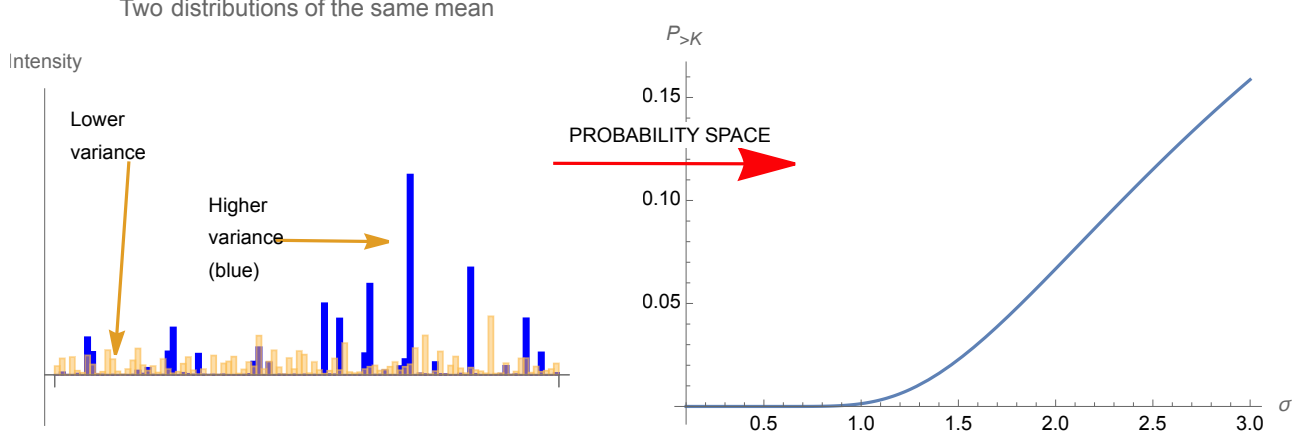
Fig. 8. (Left) An illustration of how a higher variance (hence scale), given the same mean, allow more spikes –hence an antifragile effect. We have random paths of two gamma distribution of same mean, different variances, $X_1 \sim G(1,1)$ and $X_2 \sim G(\frac{1}{10}, 10)$, showing higher spikes and maxima for X_2. The effect depends on norm $||.||_\infty$, more sensitive to tail events, even more than just the scale which is related to the norm $||.||_2$. (Right) Representation of Antifragility of (Left) in distribution space: we show the probability of exceeding a certain threshold for a variable, as a function of σ the scale of the distribution, while keeping the mean constant.
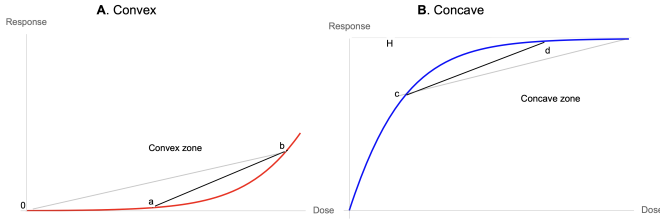

Fig. 9. (A) Every (relatively) smooth dose-response with a floor has to be initially convex, hence prefers variations and concentration. (B) Every (relatively) smooth dose-response with a ceiling has to be concave while approaching the ceiling, hence prefers stability.
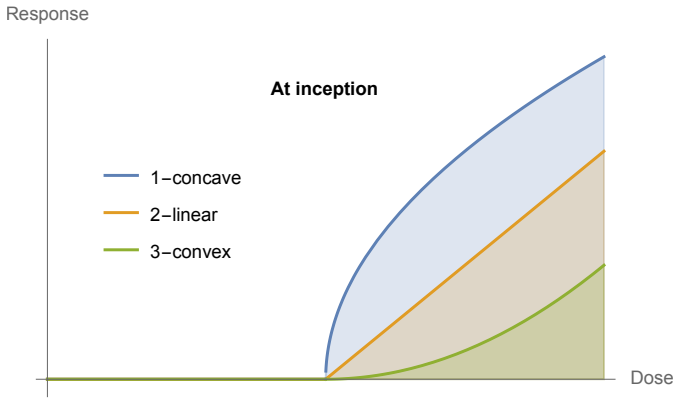

Fig. 10. The three possibilities at inception

appear, under scrutiny, to belong to the first two cases, one cannot exclude them from analysis. We note that given that the inception of these curves is 0, no linear combination can be initially convex unless the curve is convex, which would not be the case if the start of the reaction is at level different from 0.

There are many sub-classes of functions producing a sigmoidal effect. Examples:

- Pure sigmoids with smoothness characteristics expressed in trigonometric or exponential form, $f : \mathbb{R} \to [0,1]$:

$$f(x) = \frac{1}{2} \tanh\left(\frac{\kappa x}{\pi}\right) + \frac{1}{2}$$

$$f(x) = \frac{1}{1 - e^{-ax}}$$

- Gompertz functions (a vague classification that includes above curves but can also mean special functions)
- Special functions with support in $\mathbb{R}$ such as the Error function $f : \mathbb{R} \to [0,1]$

$$f(x) = -\frac{1}{2}\text{erfc}\left(-\frac{x}{\sqrt{2}}\right)$$

- Special functions with support in $[0,1]$, such as $f : [0,1] \to [0,1]$

$$f(x) = I_x(a,b),$$

where $I_{(.)}(.,.)$ is the Beta regularized function.
- Special functions with support in $[0,\infty)$

$$f(x) = Q\left(a, 0, \frac{x}{b}\right)$$

where $Q(.,.,.)$ is the gamma regularized function.
- Piecewise sigmoids, such as the CDF of the Student Distribution

$$f(x) = \begin{cases} \frac{1}{2} I_{\frac{\alpha}{x^2+\alpha}}\left(\frac{\alpha}{2}, \frac{1}{2}\right) & x \leq 0 \\ \frac{1}{2}\left(I_{\frac{x^2}{x^2+\alpha}}\left(\frac{1}{2}, \frac{\alpha}{2}\right) + 1\right) & x > 0 \end{cases}$$
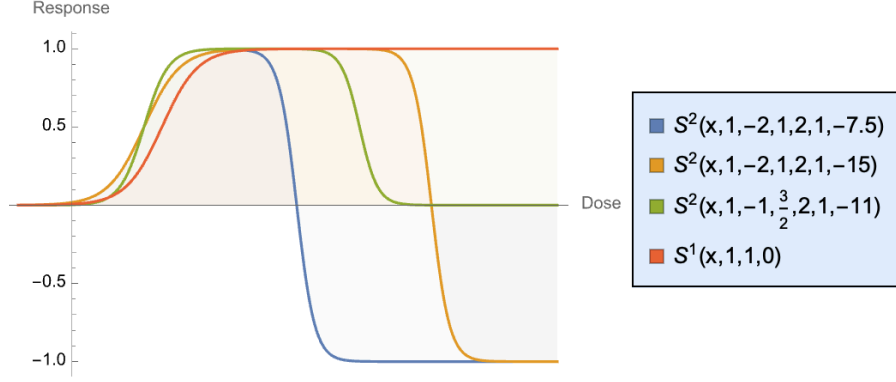
Fig. 11. Generalizing the Dose Response Curve, $S^2\left(x; a_1, a_2, b_1, b_2, c_1, c_2\right)$, $S^1\left(x; a_1, b_1, c_1\right)$ The convex part in the increasing section is what we call "antifragile".

We note that the "smoothing" of the step function, or Heaviside theta $\theta(.)$ produces to a sigmoid (in a situation of a distribution or convoluted with a test function with compact support), such as $\frac{1}{2}\tanh\left(\frac{\kappa x}{\pi}\right) + \frac{1}{2}$, with $\kappa \to \infty$, see Fig. 3.

F. Some necessary relations leading to a sigmoid curve

Let $f_1(x): \mathbb{R}^+ \to [0, H]$, $H \geq 0$, of class C^2 be the first order dose-response function, satisfying $f_1(0) = 0$, $f_1'(0)|= 0$, $\lim_{x \to +\infty} f_1(x) = H$, monotonic nondecreasing, that is, $f_1'(x) \geq 0 \; \forall x \in \mathbb{R}^+$, with a continuous second derivative, and analytic in the vicinity of 0. Then we conjecture that:

A- There is exist a zone $[0, b]$ in which $f_1(x)$ is convex, that is $f_1''(x) \geq 0$, with the implication that $\forall a \leq b$ a policy of variation of dosage produces beneficial effects:

$$\alpha f_1(a) + (1-\alpha)f_1(b) \geq f_1(\alpha a + (1-\alpha)b), 0 \leq \alpha \leq 1.$$

(The acute outperforms the chronic).

B- There is exist a zone $[c, H]$ in which $f_1(x)$ is concave, that is $f_1''(x) \leq 0$, with the implication that $\exists d \geq c$ a policy of stability of dosage produces beneficial effects:

$$\alpha f_1(c) + (1-\alpha)f_1(d) \leq f_1(\alpha c + (1-\alpha)d).$$

(The chronic outperforms the acute).

IV. The Generalized Dose Response Curve

Let $S^N(x): \mathbb{R} \to [k_L, k_R]$, $S^N \in C^\infty$, be a continuous function possessing derivatives $\left(S^N\right)^{(n)}(x)$ of all orders, expressed as an N-summed and scaled standard sigmoid functions:

$$S^N(x) \triangleq \sum_{i=1}^{N} \frac{a_k}{1 + e^{(-b_k x + c_k)}} \qquad (19)$$

where a_k, b_k, c_k are scaling constants $\in \mathbb{R}$, satisfying:

1) $S^N(-\infty) = k_L$, and
2) $S^N(+\infty) = k_R$, and (equivalently for the first and last of the following conditions)

3) $\frac{\partial^2 S^N}{\partial x^2} \geq 0$ for $x \in (-\infty, \; k_1)$, $\frac{\partial^2 S^N}{\partial x^2} < 0$ for $x \in (k_2, k_{>2})$, and $\frac{\partial^2 S^N}{\partial x^2} \geq 0$ for $x \in (k_{>2}, \infty)$, with $k_1 > k_2 \geq \ldots \geq k_N$.

By increasing N, we can approximate a continuous functions dense in a metric space, see Cybenko (1989) [18].

The shapes at different calibrations are shown in Fig. 11, in which we combined different values of N=2 $S^2\left(x; a_1, a_2, b_1, b_2, c_1, c_2\right)$, and the standard sigmoid $S^1\left(x; a_1, b_1, c_1\right)$, with $a_1 = 1$, $b_1 = 1$ and $c_1 = 0$. As we can see, unlike the common sigmoid, the asymptotic response can be lower than the maximum, as our curves are not monotonically increasing. The sigmoid shows benefits increasing rapidly (the convex phase), then increasing at a slower and slower rate until saturation. Our more general case starts by increasing, but the reponse can be actually negative beyond the saturation phase, though in a convex manner. Harm slows down and becomes "flat" when something is totally broken.

A. Antifragility and heterogeneity

Tumors are composed of a heterogeneous collection of subpopulations with varied treatment sensitivity. Given N non-interacting populations, the fragility of the total population is given by the sum of each subpopulation i's fragility, F_i, weighted by it's frequency within the total population, w_i, such that $\sum_i w_i = 1$.

$$F(\bar{x}, \sigma) = \sum_{i}^{N} w_i F_i(\bar{x}, \sigma) \qquad (20)$$

where fragility F_i for a single population is given by eqn. 1.

The simplest case of a heterogeneous mixture of two populations: sensitive (with associated dose response $H_1(x)$) and resistant ($H_2(x)$) is shown in Fig. 12A. In the case that each dose response, H_i, is non-increasing then the mixed dose response will also be non-increasing, but changes in convexity may occur. As seen in Fig. 12A, the mixed dose response has an internal plateau (shown for $w = 0.5$). Local convexity (fragility) may switch signs multiple times.
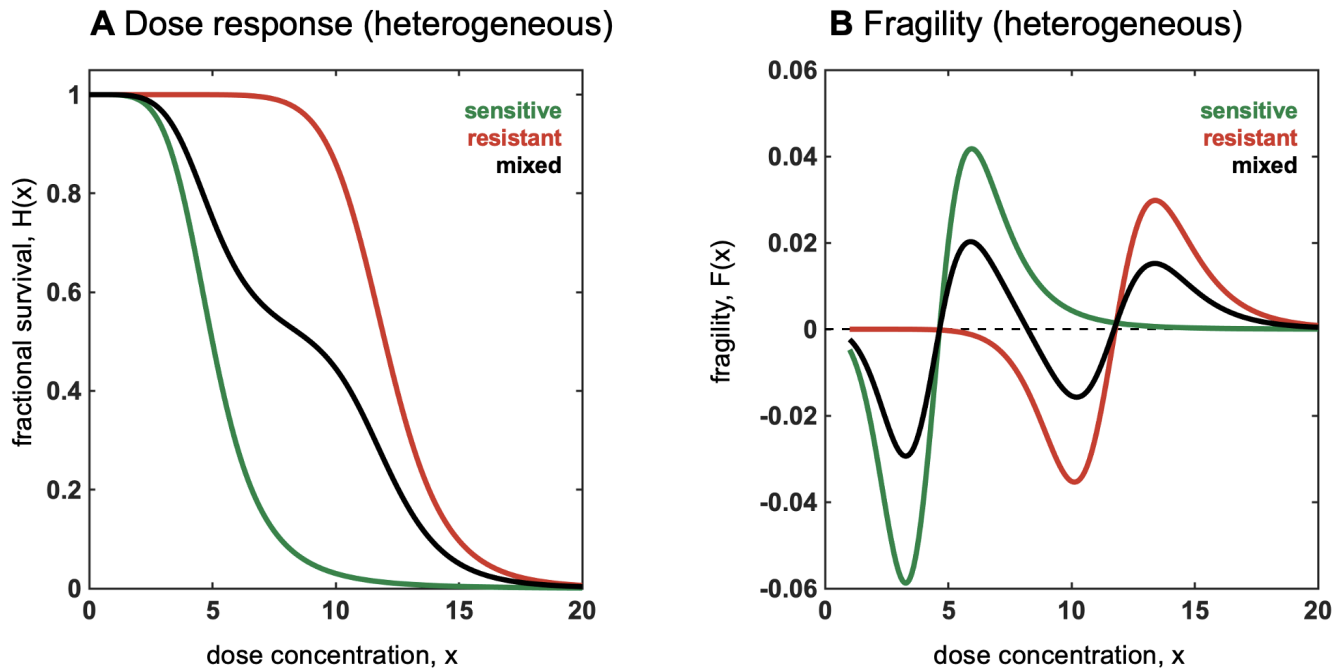
Fig. 12. **Relationship between convexity and mixed, heterogeneous populations** (A) Dose response shown for sensitive (green) and resistant (red) cell lines. When mixed, dose response is a weighted average of each (eqn. 20; black) (B) Fragility shown for sensitive (green) and resistant (red) cell lines. When mixed, fragility (black) switches from locally convex to locally concave multiple times.

V. NONLINEARITIES AND MEDICAL IATROGENICS

Next we connect nonlinearity to iatrogenics (that is, harm done by the healer) for medicine in general, broadly defined as all manner of net deficit of benefits minus harm from a given intervention.

The Taleb and Douady (2013) [68] theorems state:

- Convexity for a dose-response function increases fragility (from the expansion of the left tail in response to the increase in the scale of the distribution).
- Detection of a nonlinearity allows the prediction of fragility and helps formulate probabilistic decisions without much knowledge of the probability distribution – beyond minimum standard attributes.
- The presence of concavity in the tails of the distribution implies a silent risk.

This approach was used in stress testing by the International Monetary Fund (IMF) where the degree of concavity in the tail was used as an indicator of the severity of tail exposure, see Taleb, Canetti et al. [102].

A. Effect reversal

Radiation might be beneficial in small doses, with reversal later on. In Neumaier et al. (2012) [69] titled "Evidence for formation of DNA repair centers and dose-response nonlinearity in human cells":

> The standard model currently in use applies a linear scale, extrapolating cancer risk from high doses to low doses of ionizing radiation. However,
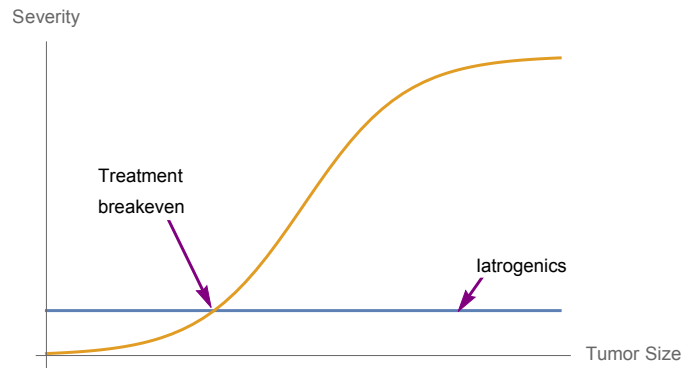
Fig. 13. Drug benefits when convex to Numbers Needed to Treat (NNT) in the left part, with gross iatrogenics invariant to condition (the constant line). We are assuming a standard sigmoidal benefit function.

our discovery of DSB clustering over such large distances casts considerable doubts on the general assumption that risk to ionizing radiation is proportional to dose, and instead provides a mechanism that could more accurately address risk dose dependency of ionizing radiation.

So low-level radiation may cause hormetic overreaction producing protective effects. Also see Tubiana et al. (2005) [70]. Bharadwaj and Stafford (2010) present similar general-sigmoidal effects in hormonal disruptions by chemicals [71].

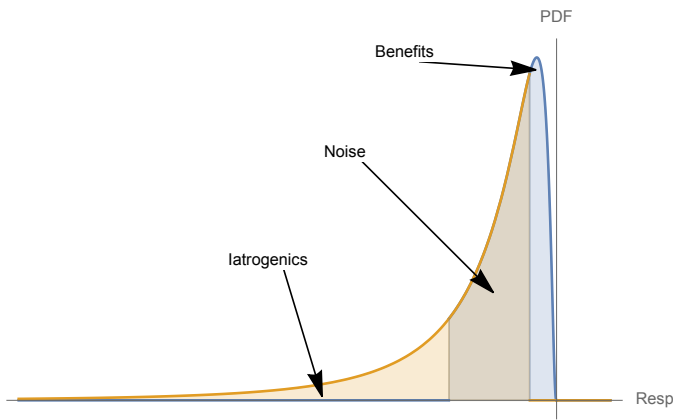Fig. 14. Unseen risks and mild gains: translation of Fig. 13 into a probabilistic representation, showing to the skewness of a decision involving iatrogenics when the condition is mild. This also gives the intuition of the Taleb and Douady[68] translation theorems from concavity for $S(x)$ into a probabilistic attributes.

B. Nonlinearity of NNT and the consequences

Below are applications of convexity analysis in decision-making in dosage, shown in Fig. 13 and Fig. 14. In short, it is fallacious to translate a policy derived from acute conditions and apply it to milder ones. Mild conditions are different in treatment from an acute one. Likewise, high risk is qualitatively different from mild risk.

There is an active literature on "overdiagnosis", see Kalager et al(2012) [72], Morell et al.(2012) [73]. The point is that treating a tumor that doesn't kill reduces life expectancy; hence the need to balance iatrogenics and risk of cancer. An application of nonlinearity can shed some light to the approach, particularly that public opinion might find it "cruel" to deprive people of treatment even if it extends their life expectancy [17].

In a similar spirit of avoiding over-treatment, adaptive therapy in metastatic castrate-resistant prostate cancer (clinical trial NCT02415621) has illustrated the feasibility of irregular treatment protocols based on algorithms that react to tumor response. Adaptive treatment protocols maintain a stable population of sensitive cells in order to suppress the emergence of resistance [94], [95]. Resistance in some cases is similar to the irreconciliable ruin of a financial "blowup" as patients may develop multi-drug resistance to structurally or functionally different drugs. Adaptive algorithms decrease the cumulative dose administered to a patient, lessening the selection for resistance [96]. While it is not an explicitly stated goal of adaptive therapy, these schedules increase both intra- and inter-patient dosing variance [97]. [7]

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[7]This year (2022) saw the publication of calls from within the FDA to revamp the dose-finding protocols to be suitable for targeted therapies[93]. Traditional dose selection protocols invented for use with cytotoxic chemotherapies may not apply to targeted therapies that have exposure-response curves which plateau at low toxicities to the patient. Differences in convexity between chemotherapies and newly developed targeted therapies leading to differing outcomes in diminished returns of dose escalation and differing curvature of dose response curves.

TABLE I
REVIEW OF MEDICAL RESEARCH ON EMBEDDED ANTIFRAGILITY

Mithridatization and hormesis Kaiser (2003) [21] , Rattan (2008) [22], Calabrese and Baldwin (2002, 2003a, 2003b) [23],[24],[25], Aruguman et al (2006) [26].

Caloric restriction and hormesis Martin, Mattson et al. (2006) [27] [1]

Cancer treatment and fasting Longo et al. (2010) [29], Safdie et al. (2009) [30], Raffaghelo et al. (2010), [31], Lee et al (2012) [32]

Aging and intermittence Fontana et al. [33]

For brain effects Anson, Guo, et al. (2003) [34], Halagappa, Guo, et al. (2007) [35], Stranahan and Mattson (2012) [36]. The long-held belief that the brain needed glucose, not ketones, and that the brain does not go through autophagy, has been progressively replaced

On yeast and longevity under restriction Fabrizio et al. (2001)[37]; SIRT1, Longo et al. (2006) [38], Michan et al. (2010) [39]

For diabetes, remission or reversal Taylor (2008) [40], Lim et al. (2011) [41], Boucher et al. (2004) [42]; diabetes management by diet alone, early insights in Wilson et al. (1980) [43]. Couzin (2008) [44] gives insight that blood sugar stabilization does not have the effect anticipated (there needs to be stressors). The ACCORD study (Action to Control Cardiovascular Risk in Diabetes) found no benefits from lowering blood glucose levels. Synthesis, Skyler et al. (2009) [45], old methods, Westman and Vernon (2008) [46]. Bariatric (or other) surgery as alternative to intermittent fasting: Pories (1995) [47], Guidone et al. (2006) [48], Rubino et al. 2006 [49]

Ramadan and effect of fasting Trabelsi et al. (2012) [50], Akanji et al. (2012). Note that the Ramadan time window is short (12 to 17 hours) and possibly fraught with overeating so conclusions need to take into account energy balance and that the considered effect is at the low-frequency part of the timescale

Caloric restriction Harrison (1984), Wiendruch (1996), Pischon (2008)

Autophagy for cancer Kondo et al. (2005) [51]

Autophagy (general) Danchin et al. (2011) [52], He et al. (2012) [53]

Fractional dosage Wu et al. (2016) [54]

Jensen's inequality in exercise Many such as Schnohr and Marott (2011) [55],intermittent extremes vs moderate physical activity

Cluster of ailments Yaffe and Blackwell (2004) [56], Alzheimer and hyperinsulenemia, Razay and Wilcock (1994) [57]; Luchsinger, Tang, et al. (2002) [58], Luchsinger Tang et al. (2004) [59] Janson, Laedtke, et al. (2004) [60].

Benefits of *some type of* stress (and convexity of the effect) For the different results from the two types of stressors, short and chronic, Dhabar (2009) "A hassle a day may keep the pathogens away: the fight-or-flight stress response and the augmentation of immune function" [61]. for the benefits of stress on boosting immunity and cancer resistance (squamous cell carcinoma), Dhabhar et al. (2010) [62], Dhabhar et al. (2012) [63] , Ansbacher et al. (2013)[64]

Iatrogenics of hygiene and systematic elimination of germs Rook (2011) [65], Rook (2012) [66] (auto-immune diseases from absence of stressor), Mégraud and Lamouliatte (1992) [67] for Helyobacter Pilori and incidence of cancer

APPENDIX

Table I reviews the medical literature on embedded antifragility, defined as indirectly producing evidence of benefits from the "disorder cluster".

To eliminate ambiguity, let us define convexity. Let $f(.)$ be the response function, $f : \mathbb{R}^+ \to \mathbb{R}$ be a twice differentiable function. If over a range x $\in [a, b]$, over a set time period Δt, $\frac{\partial^2 f(x)}{\partial x^2} \geq 0$, or more practically (by relaxing the assumptions of differentiability), $\frac{1}{2}(f(x + \Delta x) + f(x - \Delta x)) \geq f(x)$, with $x + \Delta x$ and $x - \Delta x \in [a, b]$ then there are benefits or harm from the unevenness of distribution, pending whether f is defined as positive or favorable or modeled as a harm function (in which case one needs to reverse the sign for the interpretation).

We can generalize to comparing linear combinations: $\sum \alpha_i = 1$, $0 \leq |\alpha_i| \leq 1$, $\sum(\alpha_i f(x_i)) \geq f(\sum(\alpha_i x_i))$; thus we end up with situations where, for $x \leq b - \Delta$ and $n \in \mathbb{N}$, $f(nx) \geq nf(x)$. This last property describes a "stressor" as having higher intensity than zero: there may be no harm from $f(x)$ yet there will be one at higher levels of x.

Now if X is a random variable with support in $[a, b]$ and f is convex over the interval as per above, then

$$\mathbb{E}(f(x)) \geq f(\mathbb{E}(x)), \tag{21}$$

what is commonly known as Jensen's Inequality, see Jensen(1906) [6], Fig. 5. Further (without loss of generality), if its continuous distribution with density $\varphi(x)$ and support in $[a, b]$ belongs to the location scale family distribution, with $\varphi(\frac{x}{\sigma}) =$

$\sigma\varphi(x)$ and $\sigma > 0$, then, with $\mathbb{E}_\sigma$ the indexing representing the expectation under a probability distribution indexed by the scale σ, we have:

$$\forall \sigma_2 > \sigma_1, \ \mathbb{E}_{\sigma_2}\left(f(x)\right) \geq \mathbb{E}_{\sigma_1}\left(f(x)\right) \tag{22}$$

The last property implies that the convexity effect increases the expectation operator. We can verify that since $\int_{f(a)}^{f(b)} y \frac{\phi\left(f^{(-1)}(y)\right)}{f'\left(f^{(-1)}(y)\right)} \mathrm{d}y$ is an increasing function of σ. A more simple approach (inspired from mathematical finance heuristics) is to consider for $0 \leq \delta_1 \leq \delta_2 \leq b - a$, where δ_1 and δ_2 are the mean expected deviations or, alternatively, the results of a simplified two-state system, each with probability $\frac{1}{2}$:

$$\frac{f(x - \delta_2) + f(x + \delta_2)}{2} \geq \frac{f(x - \delta_1) + f(x + \delta_1)}{2} \geq f(x) \tag{23}$$

This is of course a simplification here since dose response is rarely monotone in its nonlinearity, as we will see in later sections. But we can at least make claims in a certain interval $[a, b]$ and it can produce useful heuristics.

What are we measuring? Clearly, the dose (represented on the x line) is hardly ambiguous: any measurable quantity can do, such as systolic blood pressure, ejection fraction, caloric deficit, pounds per square inch, temperature, etc. The response, harm or benefits, $f(x)$ on the other hand, need to be equally precise, nothing vague, such as hazard ratios, some quantifiable index of health, median life expectancy, and similar quantities. If one cannot express the response quantitatively, then such an analysis cannot apply.

The authors declare no conflict of interest.

Yaneer Bar Yam and participants in the International Conference On Complex Systems, Boston, 2018 where some early ideas leading to this paper were presented [101] (synthesized in the appendices), as well as Raphael Douady, Luke Pierik, Sandy Anderson, Maximilian Strobl, and Andriy Marusyk. Editorial Note: excluding appendix and supplementary material, the overlap with this document and the conference proceedings is below 20%.

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