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Mathematical properties of Hand Incremental Effect Additivity and other synergy theories

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Synergy theories for multi-component agent combinations use 1-agent dose-effect relations (DERs), known from analyzing previous 1-agent experiments, to calculate neither-synergy-nor-antagonism combination DERs. Synergy theories are widely used in pharmacology, toxicology, and radiation biology. This article analyzes mathematical properties of one important synergy theory, proposed by John Hand in a little-known article published in 2000 and here called Hand Incremental Effect Additivity (HIEA). In 2018, Hand's approach was reinvented in a radiobiology study that inadvertently overlooked his paper. We carefully state the assumptions required for mathematically rigorous development of HIEA and other synergy theories. Under these assumptions, studying synergy/antagonism between any number of agents can be done on a single 2d plot. We show that HIEA combination DER is in general not well-defined in that it can "blow up" at finite total dose. We also formulate necessary and sufficient conditions on 1-agent DERs preventing such pathology. Using weighted harmonic means, we study the betweenness property of HIEA synergy theory and demonstrate that Hand's combination DER has a systematic tendency for betweenness violation. On the positive side, we introduce the concept of a strongly dominant agent and show that the presence of such an agent ensures the betweenness property. We show also that the betweenness property holds for another major synergy theory, Loewe–Berenbaum Additivity. Our emphasis in this article on synergy theories that can handle any number of agents was motivated by applications to the study of toxic effects of galactic cosmic rays on astronauts during interplanetary travel.

KEYWORDS
betweenness property, dose-effect relation, galactic cosmic rays, Hand Incremental Effect Additivity, Loewe–Berenbaum Additivity, neither synergy nor antagonism combination, weighted harmonic mean

MSC CLASSIFICATION
34A99, 92-08, 92F05, 92F99

1 | INTRODUCTION

1.1 | Synergy theories

When several agents act jointly on a biological object, a question of theoretical and practical importance is how to detect the presence of synergistic or antagonistic interactions between the agents based on measurements of the effect produced by various doses of these agents in experiments where the agents act either separately or in different combinations. In this article, we assume that (1) the agents have a common target, (2) their doses can be measured using the same units, and (3) the agents produce an observable effect that can be measured on the same scale. Thus, it makes sense to define the combination dose d as the sum of the individual doses.

A key idea behind the detection of interaction between N agents, $N \geq 2$, is to specify, for every collection of doses $d_1, d_2, \ldots, d_N$ of the respective agents in a combination, a certain value, $I(d_1, d_2, \ldots, d_N)$, of effect that characterizes the lack of either synergy or antagonism between the agents. If for the observed joint effect, I, we have $I > I(d_1, d_2, \ldots, d_N)$, then the combined action of the agents is assumed synergistic while if $I < I(d_1, d_2, \ldots, d_N)$, then it is viewed as antagonistic. For a review of this approach, see studies [1–5]. We will call the function $I(d_1, d_2, \ldots, d_N)$ *Neither-Synergy-Nor-Antagonism (NSNA) criterion*; another commonly used terms are *null or null reference model* [3, 5] and *non-interaction model* [1]. A specific way of defining and justifying the function $I(d_1, d_2, \ldots, d_N)$ will be referred to as a *synergy theory*. In this article, we assume dose proportions (or weights) to be fixed; see Section 1.2. In this case, the NSNA criterion depends on the total combination dose $d = \sum_{j=1}^{N} d_j$ alone, and we set $I(d_1, d_2, \ldots, d_N) = I(d)$.

Different agents, and even doses of the same agent, may compete for sensitive elements of the target, for example, enzymes and other proteins in pharmacology and toxicology and segments of DNA in radiation biology. Therefore, no interaction between agents is here understood to mean no *unexpected interaction*; see also Berenbaum [1]. A notable example of such no-interaction combination is the so-called *sham combination*, where doses of the *same* agent are combined.

Synergy or antagonism is usually thought of as a property of combined agents determined by the mechanism of their action and interaction. However, a more general situation may arise where the same group of agents may be synergistic for some ranges of effect or dose intervals and antagonistic elsewhere; see, for example, Pearson et al. and Shapovalova et al. [4, 6] and references therein.

Analyzing statistical significance of synergy or antagonism based on empirical data is beyond the scope of this work. For examples of synergy/antagonism analysis combined with statistical analysis of noised data, see [3, 5–7].

The main goal of this article is to systematically develop and study mathematical properties of *Hand Incremental Effect Additivity* (HIEA), a major synergy theory introduced in a frequently overlooked short seminal paper by John Hand [8] and recently independently rediscovered in Ham et al. [9]. HIEA theory was prominently featured in Sinzger et al. and Shapovalova et al. [5, 6]. Although Hand formulated his synergy theory for $N = 2$ agents and only considered examples of combinations of two agents, he mentioned the possibility of the extension of his synergy theory to any number of agents [8].

One notable application, see Huang et al. [7, 10], is to simulations of biological effects of galactic cosmic rays (GCRs), a mixture of a very large number of different radiations that may cause significant harm to the health of astronauts during interplanetary travel [11]. Terrestrial linear accelerator (LINAC) and other experiments simulating the action of GCR use compositions of far fewer radiations; even so, some employ 33 different beams [12]. This and other radiobiological applications color some of our methodological choices and terminology. For example, we will usually regard dose as a variable whose only allowed transformations correspond to a change in units, for example, from Gray (Gy) to centigray (cGy), that is, scaling. In radiation biology, this stringent restriction is natural because dose has a fundamental physical meaning—mean energy absorbed per unit mass. Another consequence of the abovementioned application is an emphasis on synergy theories that can readily handle combinations of many components rather than just two.

Throughout this paper, we emphasize deleterious effects and assume, in intuitive interpretations, that agents are harmful, as is the case in radiation biology and toxicology. We also intuitively interpret synergy as "bad" synergy—even more damage than expected from non-interacting agents. By changing heuristic interpretations, the formalism we discuss could instead be applied to settings where agents intended to cure are involved, as is common in pharmacology.

In this article, we only consider situations where dose is administered acutely—that is, so rapidly it can be regarded as almost instantaneous. Alternatives—including the case, very important in some applications, of a low, approximately constant dose rate—are not discussed. An important consequence of the assumption of acute dose delivery is that time variable including temporal dynamics of action and interaction between agents is not explicitly present in the discussed synergy theories. As a result, they are expected to be invariant under any permutation of agents—changing the order of agents must leave any reasonable NSNA criterion unchanged. In the case of two agents, this symmetry property is frequently, and incorrectly, called commutativity, a term reserved for the well-known algebraic property of a binary operation on a set of objects. For an extensive discussion of temporal aspects of pharmacodynamics and synergy, see a foundational article by Walter Siegfried Loewe [13].

This article is a substantially modified and expanded version of the preprint [14].

1.2 | Dose, effect, dose-effect relations (DERs), and effect-dose relations (EDRs)

Let E be a function that associates with every admissible dose d of an agent the effect, $E(d)$, produced by the agent in a biological object. Such functions are called 1-agent DERs. Synergy theories use 1-agent DERs, assumed already known due to analyzing the results of experiments where agents act alone, to derive a NSNA DER, $I(d_1, d_2, ..., d_N)$, for a combination of N agents.

Every 1-agent DER $E(d)$ is here required to be a monotonically increasing function, to have domain $[0, \infty)$, and to satisfy $E(0) = 0$. Our DERs thus always have background effect subtracted out, for our intention is to study synergy among combined agents, not synergy between known agents and typically unknown causes of effects in untreated, control targets. Our formalism can readily be adjusted to the case of decreasing DERs with a finite value of $E(0)$, a setting used, for example, in [3, 6, 15].

We regard 1-agent DERs as informed estimates based on analyzing 1-agent data but not as random functions accounting for measurement errors and other sources of stochastic variation of data used to produce statistical estimates of individual DERs.

Consider a combination of $N \geq 2$ agents. The DER, E_j, of jth agent is a function E_j: $[0, \infty) \rightarrow [0, h_j)$, where $h_j \in (0, \infty]$ is the maximum effect produced by this agent, $1 \leq j \leq N$. Let $d > 0$ be the total combination dose, $d = \sum_{j=1}^{N} d_j$. For every j, the jth agent contributes dose d_j that constitutes a fraction $r_j = d_j/d$ of the total mixture dose d, so that $d_j = r_j d$. Note that $\sum_{j=1}^{N} r_j = 1$. To avoid degenerate mixtures, we will be always assuming that $r_j > 0$ for all j, $1 \leq j \leq N$. Throughout this paper, we use without essential loss of generality the following assumption, which was also a default premise in Hand [8] and to a large extent in Sinzger et al. [5]:

Dose proportionality assumption (DPA)

Dose proportions r_j, $1 \leq j \leq N$, of the combined agents are fixed.

A convenient consequence of this assumption is that the dose of each agent is uniquely determined by the combination dose: $d_j = r_j\, d$, $1 \leq j \leq N$. In practice, to satisfy the DPA, experimental datasets should be partitioned into subsets with identical dose proportions; in the worst-case scenario, this would require conducting a separate synergy analysis for each $(N + 1)$-dimensional data point (i.e., doses of all the agents and their combined effect). Thus, employing DPA amounts to replacing analysis of an entire dataset with aggregation of the results of synergy analysis applied to individual data points or their homogeneous subsets. The abovementioned possibility of effect and/or dose-dependent synergy or antagonism makes such a replacement well-justified and sometimes even necessary. Note also that DPA represents a typical feature of radiobiological experiments including GCR studies.

If all effects in a given combination experiment are subjected to a continuous monotonically increasing transformation that leaves zero invariant, the resulting calculations will usually be considered to describe the same biological situation. Thus, allowed transformations of the effect are less stringently restricted than those for the dose.

Some examples of 1-agent DER $E(d)$ are d^a with $a > 0$; $exp(d) - 1$; $d\exp(d)$; $ln(d + 1)$; $d/(d + 1)$; a more general Hill model $E(d) = hd^a/(d^a + b)$ with a, b, $h > 0$ that is widely used in pharmacology and toxicology for describing kinetics of biochemical reactions (see, e.g., [1, 3–5, 15, 16]) and the linear-quadratic (LQ) function

$$E(d) = \alpha d + \beta d^2, \tag{1.2.1}$$

where α and β are non-negative numbers, with $\alpha + \beta > 0$. LQ functions have played a prominent role in radiobiology, including synergy modeling; see, for example, Zaider and Rossi [17]. A more sophisticated example of DER, that is nonetheless accommodated by HIEA synergy theory, is $\exp(-d^{-a})$ for $a > 0$; every such DER vanishes at $d = 0$ together with all its derivatives and is thus "extremely flat" at the origin. Notice that the range of the above DERs is an interval $[0, h)$, where $h = 1$ in the last example, is finite for the Hill model, and $h = \infty$ in all other cases.

As pointed out in previous studies [1, 5, 7] and discussed below in Section 3.4, there are substantial reasons for sometimes using effect rather than dose as the basic independent variable. In an acutely treated biological target, effects typically persist much longer than dosing—a hint that effects are perhaps more important. If a DER $E(d)$ is continuous and monotonic increasing, it has an inverse function $F(I)$, the EDR, and we will often use EDRs in our calculations.

All properties of DERs can be expressed in terms of EDRs and vice versa. Here are some examples:

(A) Let E_1 and E_2 with $E_1(0) = E_2(0) = 0$ be two continuous increasing DER functions having the same range $[0, h)$. Then $E_1(d) \le E_2(d)$ for all $d \ge 0$ if and only if $F_1(I) \ge F_2(I)$ for all $I \in [0, h)$;
(B) The graphs of two continuous increasing DER curves $E_1(d)$ and $E_2(d)$ intersect at $d = d_0 > 0$ iff the respective EDR curves $F_1(I)$ and $F_2(I)$ intersect at $I = I_0$, where $I_0 = E_1(d_0) = E_2(d_0)$;
(C) An increasing DER is convex/concave if and only if the corresponding EDR is concave/convex. This follows from the fact that the graph of a DER function $I = E(d)$ is at the same time the graph of the corresponding EDR function $d = F(I)$ if we view the I axis as the axis for independent variable. Thus, a chord generated by two distinct points on the graph of the DER function stays above/below the graph of the DER function if and only if the same chord stays below/above the graph of the EDR function.

Given N jointly acting agents, the combination DER is a function $E(d_1, d_2, ..., d_N)$ representing the combination effect produced by doses $d_1, d_2, ..., d_N$ of these agents. Thus, the aforementioned NSNA DER $I(d_1, d_2, ..., d_N)$ is the combination DER for non-interacting agents postulated by a given synergy theory. For a fixed effect $I > 0$, the set of *all* dose vectors $(d_1, d_2, ..., d_N)$ such that $E(d_1, d_2, ..., d_N) = I$ is called an *isoeffective surface* or an *isobole*, a term coined by Loewe and Muischneck [18].

If the combination DER $E(d_1, d_2, ..., d_N)$ is an increasing function in each variable with the other variables being fixed, an assumption we adopt throughout this study, then under DPA, it is a well-defined function, $E(d)$, of the total combination dose d. The inverse function will be called *combination EDR*, and its NSNA version will be denoted, as above, $I(d)$.

1.3 | Older synergy theories

1.3.1 | Simple Effect Additivity (SEA) synergy theory

Researchers in pharmacology and toxicology have known for at least 150 years [19] that the "obvious" method of analyzing combination effects with the SEA approach to synergy—namely, just adding component effects—is problematic when some 1-agent DERs are nonlinear. This problem is reviewed, for example, in [7, 15, 20].

The NSNA DER that characterizes SEA synergy theory is

$$I(d_1, d_2, ..., d_N) = \sum_{j=1}^{N} E_j(d_j),$$

or, under DPA,

$$I(d) = \sum_{j=1}^{N} E_j(r_j d). \tag{1.3.1}$$

A fundamental problem with SEA and many other synergy theories is that they fail to obey what is called the *sham combination principle*, discussed, for example, in [1, 2, 15, 21], thus making it not self-consistent. For a synergy theory to obey this principle, the theory's NSNA DER must always, for a combination of one agent with itself, give the correct answer (the value of the DER at the total combination dose). The following example shows that SEA synergy theory does not obey the sham combination principle. Suppose an agent has an LQ DER $E(d) = \alpha d + \beta d^2$ with $\beta > 0$. Regard the agent as a 1:1 mixture of two identical components, each having, therefore, the same 1-agent LQ DER. Then calculating the baseline NSNA DER for this sham combination by SEA synergy theory gives $2[\alpha(d/2) + \beta(d/2)^2] = \alpha d + \beta d^2/2$. But, of course, one cannot decrease the beam's toxicity by mental gymnastics, so the correct value is $\alpha d + \beta d^2$. More generally, applying the sham combination principle to an agent with continuous DER $E: [0, \infty) \rightarrow [0, \infty)$, we find that under SEA synergy theory, one would have $E(d_1 + d_2) = E(d_1) + E(d_2)$ for all doses $d_1, d_2 \geq 0$. It is well-known [22] that every continuous solution of this functional equation, called *Cauchy equation*, has the form $E(d) = cd$ for some $c \geq 0$. Thus, in the case of nonlinear DERs, SEA synergy theory is incompatible with the sham combination principle.

SEA synergy theory also fails to satisfy a more stringent "combination of combinations" principle. It addresses the situation where some of the agents are combinations of other agents. Such collections of agents constituting any of the original agents may overlap or contain identical agents. The combination of combinations principle posits that a joint action theory expressed in terms of the new collection of agents must agree with the original one under the usual rule for transformation of their weights. Another term used in the literature for this principle is associativity; see, for example, Berenbaum and Sinzger et al. [1, 5]. We prefer the former term because associativity is an algebraic property of a binary operation on a set while the combination of combinations property of a synergy theory is not related to any binary operation.

1.3.2 | Loewe–Berenbaum Additivity (LBA)

Many replacements for SEA have been suggested. One elegant replacement that does obey the sham combination principle is LBA introduced by Loewe in [13] and extensively studied, applied and popularized by Morris Berenbaum [1, 2, 15]. Stated for any number of agents and independently of DPA, this major synergy theory postulates the following NSNA criterion: doses $d_1, d_2, \ldots, d_N$ of $N \geq 2$ non-interacting agents produce a combined effect $I > 0$ if and only if

$$\sum_{j=1}^{N} \frac{d_j}{F_j(I)} = 1, \tag{1.3.2}$$

where F_j $[0, h) \rightarrow [0, \infty)$ is the jth agent's EDR and the range of effects, $[0, h)$, is assumed identical for all agents. Under LBA synergy theory, every isobole is a polytope in the $(N\text{-}1)$-dimensional affine hyperplane in R^N specified by Equation (1.3.2). In the case $N = 2$, the isobole is a line segment in the plane with endpoints $(0, F_2(I))$ and $(F_1(I), 0)$. If a point $(d_1, d_2, \ldots, d_N)$ experimentally found to produce effect I lies below the isobole given by Equation (1.3.2) (i.e., the LHS of this equation is <1), then LBA criterion suggests synergy while if it lies above the isobole (i.e., the LHS is >1), then it indicates antagonism.

It is readily verified that Equation (1.3.2) is satisfied for a sham mixture. More generally, as Berenbaum noted in [1], this is also true when the agents are appropriate dilutions of the same agent, assumed to be a drug or toxin. Furthermore, he argued in [1], incorrectly, that Equation (1.3.2) represents a universal NSNA criterion, the crux of his argument being that every combination of distinct agents is equivalent to a diluted sham combination. A logical error in this argument was discovered by Hand [21]. Perhaps more importantly, actual experiments with the joint action of drugs, toxins, and other agents without known interactions reveal that in many cases, isoboles are nonlinear; see, for example, Lederer et al. and Varaksin et al. [3, 23]. This calls for alternative synergy theories. One of them, HIEA, is studied in this work.

The assumption that all 1-agent DERs must have the same range can be lifted; see Section 5.3 where such an extension is carefully implemented for HIEA synergy theory. The idea of this extension is due to Hand [8]. The same idea works equally well for LBA, compare with Lederer et al. and Sinzger et al. [3, 5].

1.3.3 | Specialized synergy theories

There are other suggested replacements for SEA synergy theory that obey the sham combination principle and are useful but are applicable only if all 1-agent DERs in a combination have a specific functional form—such as LQ functions; see Equation (1.2.1). Examples include the formalisms described in [17, 24, 25]. Our paper will not discuss these specialized synergy theories further, focusing instead on the more flexible LBA and HIEA formalisms.

1.4 | Novelty of this work

Scattered throughout the voluminous literature on synergy theories are a multitude of approaches, viewpoints, and results, some of them controversial. Therefore, for clarity and reader's benefit, we list below novel contributions of this work, to the best of our knowledge.

(1) As stated in Section 1.1, the principal motivation for our article is applications to radiation biology including, most notably, effects of multi-agent GCRs on astronauts on an interplanetary trip. Therefore, we only considered synergy theories, specifically LBA and HIEA, that are readily applicable to any number of agents. The bulk of literature on synergy theory deals with the case of two agents.
(2) We introduced general monotonicity and smoothness conditions on individual and combination DERs or EDRs from which various properties of LBA and HIEA synergy theories can be derived through rigorous mathematical arguments.
(3) The combined action of $N \geq 2$ agents is traditionally represented graphically as a response surface in the $(N + 1)$—dimensional space, where the first N dimensions represent the doses of individual agents and the last dimension is used for the combined effect. This has limited many synergy studies to the case of two agents [3–5, 26]. Here, we systematically use a different method for representing the effects of any number of agents, acting either separately or in combination, as a 2d plot. The method consists of representing EDRs of individual agents on the same (effect, dose) axes and superimposing on it, using the same axes, the (combined effect, total dose) plot for the agents' joint action under the NSNA assumption. This enables visualizing and comparing EDRs or DERs of any number of agents and studying the position of the combination NSNA EDR (or DER) relative to those of individual agents. The superimposition of the joint action plot on 1-agent EDR plots is enabled by two premises: (1) DPA and (2) the assumption that the combination DER $E(d_1, d_2, ..., d_N)$ is an increasing function in each dose variable; see section 1.2. These assumptions make the combination DER a monotonic function of the total combination dose, d, alone.
(4) We introduced the formalism of weighted harmonic means (WHM) that allows for convenient formulation and analysis of LBA, HIEA, and other synergy theories under DPA.
(5) We showed that in general, the NSNA HIEA EDR of agents with the same range of effects is not well-defined, an important observation that was overlooked by the author of HIEA synergy theory [8] and those who studied and utilized it. In terms of agents' DERs, assuming they are defined for all doses $d \geq 0$, this means that the combination DER may “blow up” at a finite dose, see Example 1 in Section 4.2. Furthermore, we formulated a necessary and sufficient condition that precludes the occurrence of this pathology; see Proposition 4.2.2. Interestingly, this condition is free of dose proportions and only involves the agents' EDRs.
(6) In the case of agents with distinct ranges of effect considered in [3, 5, 8] (or, borrowing the terminology from Sinzger et al. [5], combinations of full and partial agents), we formulated a new condition, see condition (d) in Section 5.3, required for mathematical consistency of HIEA synergy theory.
(7) We studied the betweenness property of LBA and HIEA synergy theories. This property states that the DER (or EDR) of a combination of $N \geq 2$ noninteracting agents must be contained between the maximum and minimum of the individual DERs (or EDRs). We showed that the betweenness property holds for LBA; see Section 2. We also found that while the NSNA HIEA combination EDR always stays below the maximum of individual DERs, it has a systematic tendency to go below the minimum of individual EDRs on a certain interval of doses. Moreover, in some cases, such dose interval may be infinite. Violation of the betweenness property is a major shortcoming of HIEA synergy theory.
(8) We introduced in Section 5.2 the concept of a strongly dominant agent, which is consequential both for theory and applications. In particular, we showed that the presence of a strongly dominant agent implies the betweenness property of the HIEA NSNA combination EDR; see Proposition 5.2.3.
(9) We extended in Section 5.1 the similarity theory introduced in Berenbaum [1] and further discussed in other works [2, 3, 5]. In the general setting considered in Section 5.1, DERs, $E_j(d)$, of individual agents are obtained through double scaling of a given function g, that is, $E_j(d) = P_j\, g\,(C_j\, d),\ 1 \leq j \leq N$, with $P_j,\ C_j > 0$. In a number of particular cases including the case of power function g, we found the combination HIEA DER or EDR in closed form. Previously, the similarity theory was studied in the case $P_j = 1,\ 1 \leq j \leq N$, that is, for agents with constant potency ratios C_i/C_j.

1.5 | Acronyms and terminology

The following acronyms and terminology emphasize concepts that are central in this paper:

DER—dose-effect relation; **DPA**—dose proportionality assumption; **EDR**—effect-dose relation; **ESF**—effect sensitivity function (the reciprocal of the derivative of an EDR); **GCR**—galactic cosmic ray(s); **HIEA**—Hand Incremental Effect Additivity; **IVP**—initial value problem; **LBA**—Loewe–Berenbaum Additivity; **LQ**—linear-quadratic DER; **NSNA**—neither synergy nor antagonism; **ODE**—ordinary differential equation; **SEA**—simple effect additivity; **WHM**—weighted harmonic mean.

1.6 | Preview

Section 2 below describes a WHM approach to LBA and establishes the betweenness property. The focus in Section 3 is on basic concepts and equations of HIEA synergy theory and its heuristic justification. It also showcases a motivating example of carcinogenic effects of GCR and an illustrative example comparing SEA, LBA, and HIEA synergy theories. A detailed mathematical analysis of HIEA synergy theory is contained to Sections 4 and 5. The final section, Discussion and Conclusions, provides a summary and delivers a broader perspective.

2 | LBA UNDER DPA: WHM APPROACH

For any weights $r_j > 0$, $1 \le j \le N$, such that $\sum_{j=1}^{N} r_j = 1$, the WHM of a vector $\mathbf{x} = (x_1, x_2, \ldots, x_N)$ with positive components is defined by

$$H(\mathbf{x}, \mathbf{r}) := \left(\sum_{j=1}^{N} \frac{r_j}{x_j} \right)^{-1}.$$

Clearly, it satisfies the inequalities

$$\min\{x_j : 1 \le j \le N\} \le H(\boldsymbol{x}, \boldsymbol{r}) \le \max\{x_j : 1 \le j \le N\}, \tag{2.1}$$

both of which are strict unless all components of vector $\mathbf{x}$ are equal.

Under DPA, Equation (1.3.1) can be represented in an equivalent form

$$\sum_{j=1}^{N} \frac{r_j}{F_j(I)} = \frac{1}{d}. \tag{2.2}$$

Let

$$\frac{1}{F(I)} = \sum_{j=1}^{N} \frac{r_j}{F_j(I)}. \tag{2.3}$$

Observe that $F(I)$ for $I > 0$ represents the WHM of the vector $(F_1(I), F_2(I), \ldots, F_N(I))$. Function $F(I)$ is called *the combination EDR*. The properties of the combination EDR are stated in the following proposition, which proof is based on inequalities (2.1) and Equation (2.3).

Proposition 2.1. *Suppose 1-agent DERs E_j: $[0, \infty) \to [0, h)$ are continuous and monotonic increasing functions with the same finite or infinite range $[0, h)$ and satisfy the condition $E_j(0) = 0$, $1 \le j \le N$. Then Equation (2.3) determines a unique continuous and monotonic increasing combination EDR F: $[0, h) \to [0, \infty)$ such that*

$$min\{Fj(I) : 1 \le j \le N\} \le F(I) \le max\{Fj(I) : 1 \le j \le N\} \; for\, all\, I \in [0, h), \tag{2.4}$$

where either equality holds for all $I \ge 0$ iff all DERs E_j, $1 \le j \le N$, are identical.

Inequalities (2.4) and equivalent inequalities

$$\min\{E_j(d) : 1 \le j \le N\} \le E(d) \le \max\{E_j(d) : 1 \le j \le N\} \text{ for all } d \ge 0,$$

where $E = F^{-1}$ is called the *combination* DER, constitute the *betweenness property*. This property is an important advantage of LBA over some other synergy theories including HIEA; see Section 5.2. An intuitive interpretation of betweenness is that a combined effect of the total dose d of non-interacting agents should be in some sense an average of the component effects of the same dose d.

Suppose an experiment with agent doses $d_1, d_2, \ldots, d_N$ produces a combined effect I. If $I > E(d)$, where d is the total combination dose, or equivalently $F(I) > d$, then the NSNA LBA criterion given by Equation (2.2) predicts synergy while if $I < E(d)$ or equivalently $F(I) < d$, then it points to antagonism; see Figure 1.

Finally, the validity of the combination of combinations property for LBA synergy theory follows from Equation (2.3) through a fairly trivial exercise in linear algebra.

3 | THE BASICS OF HIEA SYNERGY THEORY

3.1 | Assumptions on DERs

Recall that by definition, a 1-agent DER $E(d)$ has domain $[0, \infty)$ and obeys $E(0) = 0$. Most synergy theories including LBA require additional conditions, notably continuity and monotonic increase, on DERs. Because the behavior of any 1-agent DER at very small doses cannot be empirically determined with certainty, in this article, we seek to avoid imposing strong assumptions on such behavior including differentiability of DERs at $d = 0$. Henceforth, we make the following requirements:

(a) Each 1-agent DER function $E_j(d)$ is continuous at $d = 0$ and satisfies $E_j(0) = 0$, $1 \le j \le N$;
(b) Every DER E_j is piecewise continuously differentiable on $(0, \infty)$ with no more than finitely many points of discontinuity of the derivative E_j' on any finite interval $(0, A)$;
(c) For each j, $E_j'(d)$ is finite and positive for all $d > 0$, where the derivative may be one- or two-sided.

In what follows, we will consider first a simpler case where all 1-agent DERs have the *same* range $[0, h)$, where h is finite or infinite. A more general case of distinct ranges will be addressed in Section 5.3.

Observe that if φ is a C^1-diffeomorphism of $[0, h)$, then functions $\varphi \circ E_j$ satisfy conditions (a)–(c) and can therefore serve as DERs. This allows one to standardize, in certain settings, the range of effect to [0,1) or $[0, \infty)$. Conditions (a)–(c) also hold for the functions $E_j \circ \psi$, where ψ is a C^1-diffeomorphism of $[0, \infty)$. As indicated in Section 1.1, in most

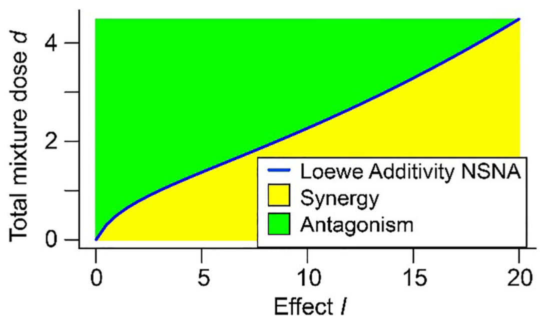

FIGURE 1 Interpreting the Loewe–Berenbaum Additivity NSNA EDR. For acronyms used in this caption, see Section 1.5. Figure 1 is hypothetical. The LBA NSNA EDR shown (dark blue curve) used Equation (2.3) to estimate the NSNA mixture dose needed to produce a given effect. If a combination experiment were to find that a combination dose smaller than the NSNA dose produces a given effect, that would indicate extra potency in the mixture not expected from analyzing the action of individual agents, that is, synergy. Hence, the location in the dose-effect plane of the synergy and antagonism regions. As always in the context of analyzing damaging agents, synergy would count as "bad" synergy. Effect is here taken as the independent variable and dose as the dependent variable. The advantages of such a switch are discussed in Section 3.4. [Colour figure can be viewed at wileyonlinelibrary.com]

cases, such transformations ψ are limited to dilations. Finally, under assumptions (a)–(c), DERs E_j are bijective and, importantly, the corresponding EDR functions F_j: $[0, h) \rightarrow [0, \infty)$, where $F_j = E_j^{-1}$, also meet conditions (a)–(c).

3.2 | The HIEA equation, its historical roots, and heuristic justification

HIEA synergy theory posits that, in the absence of synergy and antagonism between the agents, the NSNA DER function $I(d)$ for the mixture of $N \geq 2$ agents with fixed fractional dose weights r_j, $1 \leq j \leq N$, is the solution of the following autonomous IVP:

$$I' = \sum\nolimits_{j=1}^{N} r_j E_j'\left[E_j^{-1}(I)\right]; \quad I(0) = 0. \tag{3.2.1}$$

Using $E_j'\left[E_j^{-1}(I)\right]$ with I the combined effect in Equation (3.2.1) is the key assumption of HIEA synergy theory. The term "incremental" in HIEA refers to the fact that this synergy theory is defined in terms of the first derivatives of 1-agent DERs.

The idea underlying HIEA synergy theory was first proposed in the context of radiation biology by the radiobiologist G.K. Lam in [27]—a one-ion DER slope defines a *linear* relation between a sufficiently small dose increment and the corresponding effect increment, thereby to some extent circumventing the nonlinearities that plague SEA synergy theory. The Lam's replacement for SEA proposed in [28], however, does not obey the sham combination principle. Hand's brief explanation of his synergy theory, see [8], combines Lam's idea with DPA and makes the current combined effect rather than dose the basic independent variable. Because effect is a systemic property and d is not, this switch represents an important improvement conceptually. Sinzger et al. [5] derived the Hand's NSNA equation for $N = 2$ agents from the dose-equivalence formalism developed by Tallarida [29].

In applications to radiobiology, Equation (3.2.1) can be interpreted heuristically as follows [9]. Suppose a biological target is exposed to a joint action of several ionizing radiations (typically photons or ion beams). As the total combination dose d increases slightly, every individual component dose d_j has a slight proportional increase since $d_j = r_j\, d$. Therefore, every component contributes some incremental effect. The size of the incremental effect is determined by the state of the biological target, specifically by the total effect already contributed by all the components acting jointly—and *not* by the dose (or the effect) the individual component has already contributed. This current total effect determines in turn each component's incremental effect.

3.3 | An EDR formulation of the HIEA equation

Recall that the inverse function, F_j, for jth agent's DER, E_j, is called the agent's EDR. By the formula for the derivative of the inverse function, we have for $I > 0$

$$F_j'(I) = \frac{1}{E_j'\left[E_j^{-1}(I)\right]}, \; 1 \leq j \leq N.$$

For the combination EDR, $d = F(I)$, and combination DER, $I = E(d)$, we have a similar relationship

$$F'(I) = \frac{1}{E'\left[E^{-1}(I)\right]} \tag{3.3.1}$$

provided that function E has properties (a)-(c) from section 3.1. Therefore, Equation (3.2.1) that defines HIEA synergy theory can be represented in the following equivalent form:

$$\frac{1}{F'(I)} = \sum\nolimits_{j=1}^{N} \frac{r_j}{F_j'(I)}, I > 0; \quad F(0) = 0. \tag{3.3.2}$$

This is the EDR version of the HIEA equation. Recall that the combination NSNA HIEA DER and EDR depends on the weights $r_1, r_2, \ldots, r_N$, although in view of DPA this dependence is not shown explicitly.

From Equation (3.3.2), the combination EDR can formally be found by integration:

$$F(I) = \int_0^I \left[\sum_{j=1}^{N} \frac{r_j}{F_j'(x)}\right]^{-1} dx. \tag{3.3.3}$$

Under which conditions function F actually represents a solution to Equation (3.3.2) will be investigated in Section 4.2.

3.4 | Comparison of DERs and EDRs

In spite of theoretical equivalence between DERs and EDRs, the combination EDR function F given by Equation (3.3.3) has a number of practical advantages over the combination DER function E defined as a solution of the IVP (3.2.1):

(1) The derivatives of all 1-agent EDR functions in Equation (3.3.2) are evaluated at the same effect I while in Equation (3.2.1), the derivatives of 1-agent DERs are evaluated at different doses. This facilitates establishing various properties of NSNA combination DERs and EDRs. One of them is the invariance of the NSNA criterion (3.3.2) under C^1-diffeomorphisms of the effect range $[0, h)$. In fact, if φ is such a diffeomorphism, then a routine application of the Chain Rule would show that if EDR functions F_j, $1 \le j \le N$, and F satisfy Equation (3.3.2), then so do functions $F_j \circ \varphi$, $1 \le j \le N$, and $F \circ \varphi$. Establishing an equivalent invariance property for Equation (3.2.1) requires more work. The same is true for the combination of combinations property whose verification for HIEA theory based on Equation (3.3.2) amounts to application of the same trivial exercise in linear algebra that established this property for LBA based on Equation (2.3).

(2) Under a certain condition stated in Section 4.1, combination EDR can directly be found by integration; see Equation (3.3.3). As shown in Section 4.1, this circumvents under conditions (a)–(c) subtle questions about the existence, uniqueness, and regularity of the solution to the IVP (3.2.1).

(3) In many cases, the combination EDR can, while the combination DER cannot, be computed in closed form. Many examples illustrating this phenomenon will come to light in what follows. The advantage of closed forms is that they give insights into analytic and statistical properties of combination EDR as a function defined on the entire parameter space, a job for which purely numerical methods are ill-suited. That is why most of the figures illustrating our results in this article display EDR plots.

3.5 | A motivating example: carcinogenic effects of GCRs

Astronaut voyages to the moon and Mars are pending. Once a spacecraft reaches interplanetary space, that is, the solar system outside the shielding effects of the earth's atmosphere and magnetic field, astronauts will be endangered by GCRs, a complex mixture of more than 100 ionizing radiations. GCR includes atomic nuclei traveling at a speed close to the speed of light. One of the most concerning effects of GCR on astronauts is that they could develop cancer.

A recent NASA Space Radiation Laboratory experiment used silicon (^{28}Si) and iron (^{56}Fe) nuclei beams in the mile-long particle accelerator at Brookhaven National Laboratory. In order to mimic the action of GCR mixtures as closely as possible, the two beams were administered in rapid succession. The beams were designed to deposit equal doses thus forming a 1:1 mixture.

The targets of the ion beams were the Harderian glands (HGs), one near each eye, in live mice. The effect of a 1-ion or ion mixture exposure was computed as the difference between the observed HG tumor prevalence and the sporadic background prevalence. The first (radiogenic) prevalence is defined as the fraction of irradiated mice that developed at least one HG tumor while the sporadic prevalence is the fraction of unirradiated matching mice that developed at least one HG tumor in specially designed control experiments.

The 1-ion DERs for silicon and iron beams were obtained from a data set resulting from 52 1-ion experiments described in Huang et al. [7]. In these experiments, mice were exposed to various doses of 10 different ions. Along with the dose, an important variable that determines the effect of a given ion beam is linear energy transfer (LET) denoted L, measured in units keV/μm, and defined as the average amount of energy deposited per unit length of ion tracks traversing the target. For example, the respective values of LET for ^{28}Si and ^{56}Fe ion beams used in the mixture experiment were $L = 70$ and $L = 193$ keV/μm.

The 1-ion DERs were assumed to be of the form $E(d) = 1\text{-}exp(-\gamma L e^{-\delta L} d)$ with adjustable coefficients $\gamma,\ \delta > 0$ shared by the two ions, so that

$$F(I) = -\frac{e^{\delta L}}{\gamma L}\ln(1-\mathrm{I}), \quad 0 \le I < 1. \tag{3.5.1}$$

The values of coefficients γ and δ, estimated from the aforementioned 52 1-ion experiments through weighted least-squares regression, were $\gamma = 1.091 \times 10^{-4}$ μm/(keV × cGy) and $\delta = 3.941 \times 10^{-3}$ μm/keV; see Huang et al. [7].

The two 1-ion EDRs for ^{28}Si and ^{56}Fe beams (green and blue curves, respectively) and the mixture NSNA HIEA EDR (red curve) computed through Equation (3.3.3) are shown in Figure 2. Equation (3.5.1) implies that both 1-ion EDRs are convex. The outcome of the mixture experiment is depicted as a black dot. The latter lies close to the mixture NSNA HIEA curve, which, according to HIEA theory, allows one to conjecture that there is no substantial unexpected synergistic interaction between the two ion beams.

Examining Figure 2 leads to the following conclusions:

(1) The EDR curve for ^{28}Si ions lies above the EDR curve for ^{56}Fe, at least for effects between 0 and ~0.23 where the green curve becomes so high it leaves the figure. Equivalently, the DER curve for ^{28}Si ions lies below the DER curve for ^{56}Fe (at least for doses between 0 and 45 cGy). In other words, among these two particular ion beams, ^{56}Fe produces greater effect for the same dose than ^{28}Si and is thus a *dominant* agent. Additionally, on the same interval of effects, the slope of EDR curve for ^{28}Si is larger than the slope of EDR curve for ^{56}Fe, as exemplified by black tangent lines to the two EDR curves (shifted downwards for better visualization) for the effect $I = 0.15$. Equivalently, the reverse ordering of slopes holds for the two DERs. We will indicate this by saying that ^{56}Fe is a *strongly dominant* agent. The presence of a strongly dominant agent can be explained on the basis of Equation (3.5.1). In fact, this formula implies that the agent with a larger ratio $e^{\delta L}/L$ must be strongly dominant. Furthermore, for EDRs given by Equation (3.5.1), larger slope at one particular effect implies the same for all effects. Finally, it follows by integration of the derivatives of two 1-agent EDRs that strong dominance implies dominance.

(2) The mixture NSNA HIEA EDR (and DER) curve stays between the 1-ion EDRs (and DERs) for the indicated ranges of doses and effects, that is, has the *betweenness* property.

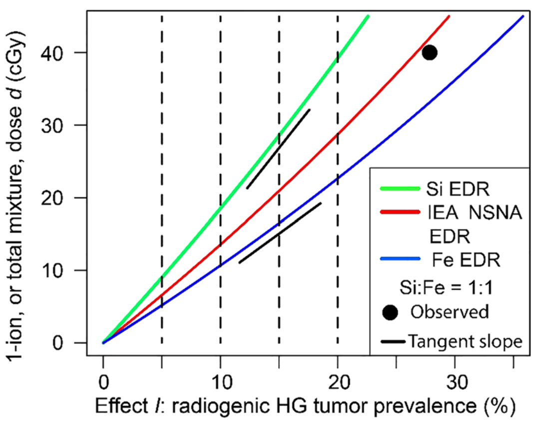

FIGURE 2 Modelling radiation mixture that has a strongly dominant Fe ion beam. For acronyms used in this caption, see Section 1.5. EDRs of ^{28}Si ion beam, ^{56}Fe ion beam, and their 1:1 mixture are represented by green, blue, and red curves, respectively. Note that all three curves are convex. The corresponding DERs are represented by the same curves if one views the vertical axis as an axis for independent variable *d*. The EDR curve for ^{28}Si ion beam lies above the EDR curve for ^{56}Fe ion beam (equivalently, DER curve for ^{56}Fe ion beam lies above the DER curve for ^{28}Si ion beam), which indicates that ^{56}Fe is a dominant agent. The same ordering holds for the derivatives of the two 1-ion EDR functions indicating that ^{56}Fe is a strongly dominant agent. It can be shown that strong dominance implies dominance. The strong dominance property follows from comparison of the slopes of black tangent lines (shifted downwards for better visualization) to the 1-ion EDR curves for the effect $I = 0.15$. The mixture HIEA (= IEA) NSNA EDR (and DER) curve stays between the two 1-ion EDR (and DER) curves, which signifies the betweenness property. The black dot represents the outcome of the mixture experiment. Its proximity to the mixture HIEA NSNA curve indicates that HIEA synergy theory points to the lack of substantial unexpected interaction between the two ion beams. For more details, see Section 3.5. [Colour figure can be viewed at wileyonlinelibrary.com]

These two conclusions motivate our study of mathematical properties of HIEA synergy theory in Sections 4 and 5. In particular, they lead to the following questions:

(A) Under what conditions is the mixture NSNA HIEA EDR $F(I)$ finite for all relevant effects I?
(B) What conditions on 1-agent DERs (or EDRs) imply the betweenness property for all $d > 0$ (or all allowed effects I)? In particular, does the betweenness property hold when one agent is dominant or strongly dominant?

3.6 | Preview example: Solving NSNA equations for three synergy theories

As a preview of the examples discussed in Section 5, Figure 3 presents an example of a 4-component mixture where each component agent contributes equally to the total mixture dose and has a smooth, monotonic increasing DER. Two of the 1-agent DERs are concave; two are convex. Figure 3 features NSNA curves obtained using three different synergy theories (SEA, LBA, and HIEA).

4 | MATHEMATICAL THEORY OF THE HIEA EQUATION

4.1 | Equation for the effect sensitivity function (ESF) and its solution

The basic HIEA equation, Equation (3.2.1), can be applied to a single agent with DER $I = E(d)$, which yields

$$I' = E'\left[E^{-1}(I)\right]; \quad I(0) = 0. \tag{4.1.1}$$

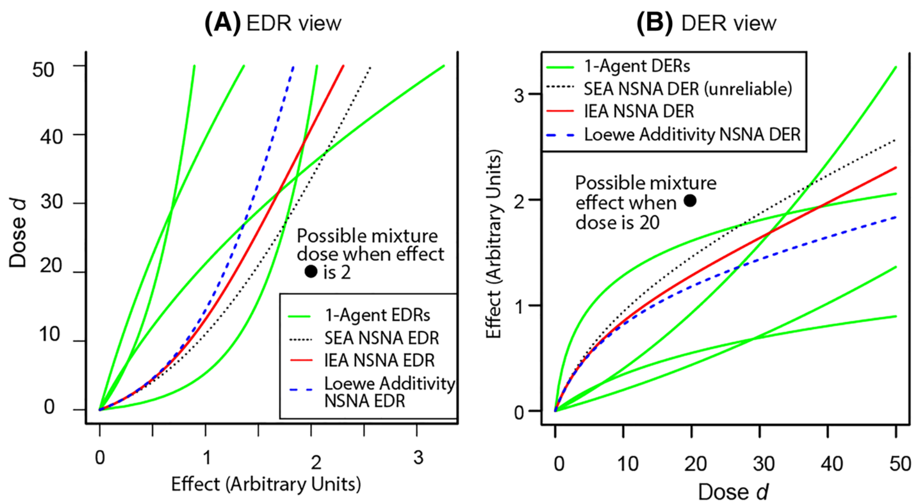

FIGURE 3 1-agent and NSNA EDRs and DERs for a four-agent combination. For acronyms used in this caption, see Section 1.5. Panel A. Each 1-agent EDR curve shows the dose that would be needed if that agent produced a given effect by itself. The SEA, LBA, and HIEA (=IEA) NSNA EDRs are calculated from the component DERs or EDRs using Equations (1.3.1), (2.3), and (3.3.3), respectively. It is seen that the SEA NSNA EDR lies beneath all four 1-agent EDRs in an interval centered near effect $I = 3$ and dose $d = 2$ exemplifying the fact that when the 1-agent DERs are highly nonlinear, as they are here, SEA should not be used. For each synergy theory, an experimental combination dose below the NSNA curve (black dot) would lie in the synergy region—less dose than expected from the component EDRs can produce a given effect—and this counts as "bad" synergy, since we deal with deleterious effects. In this paper, we did not discuss how far below an NSNA EDR curve a dose has to lie to qualify as statistically significant synergy. Thus, no error bars are shown for the dot. The NSNA LBA curve lies between the lowest and highest 1-agent EDRs at each dose, exemplifying the betweenness property; see Proposition 2.1. The HIEA curve here has this same betweenness property, and in general, an HIEA NSNA curve can never lie above the highest 1-agent EDR; see Section 5.2. Unfortunately, as also shown in Section 5.2, it can sometimes lie below the lowest—even here, in panel A, it comes close to doing so in the same interval where SEA violates the betweenness property. Panel B contains exactly the same information as panel A. Since an EDR is the inverse function of a DER, plotting DERs instead of EDRs merely involves a switching of horizontal and vertical axes, which induces diagonal reflection of curves. [Colour figure can be viewed at wileyonlinelibrary.com]

In this equation, the derivative of the agent's DER is expressed through the effect rather than dose. Following [5] the function

$$S(I) = E'\left[E^{-1}(I)\right] = \frac{1}{F'(I)} \tag{4.1.2}$$

associated with a given agent will be called the agent's ESF. In terms of ESFs, Equation (3.2.1) takes on the form

$$I' = \sum\nolimits_{j=1}^{N} r_j S_j(I); \quad I(0) = 0,$$

where S_j is the jth agent's ESF. Thus, the ESF form of Equation (3.2.1) becomes

$$I' = S(I);\ I(0) = 0, \tag{4.1.3}$$

where

$$S = \sum\nolimits_{j=1}^{N} r_j S_j \tag{4.1.4}$$

is the ESF for a combination of N agents.

In this section, we develop a mathematical theory of Equation (4.1.3) focusing on the existence, uniqueness, and specific form of its solution. The main result is given by the following theorem, which represents a formal justification for the method of separation of variables for the IVP (4.1.3).

Theorem 4.1. *Suppose S: $(0, \infty) \to (0, \infty)$ is a continuous function such that*

(a) $\int_0^x \frac{du}{S(u)} < \infty$ *for all* $x > 0$ *and*
(b) $\int_0^\infty \frac{du}{S(u)} = \infty$.

Then the inverse function to

$$F(x) = \int_0^x \frac{du}{S(u)}, \quad x > 0, \tag{4.1.5}$$

represents a unique solution I of the IVP (4.1.3) defined on $[0, \infty)$ and such that $I(x) > 0$ for $x > 0$.

Proof. Set $F(0) = 0$. It follows from the assumptions of the theorem that function F is strictly increasing, continuous at $x = 0$, continuously differentiable on $(0, \infty)$, and has $[0, \infty)$ as its range. Thus, F: $[0, \infty) \to [0, \infty)$ is a bijection. Denote by I the inverse function for F. Then $I(0) = 0$, $I(d) > 0$ for all $d > 0$, and for every $d > 0$, we have in view of the formula for the derivative of the inverse function and Equation (4.1.5)

$$I'(d) = \frac{1}{F'(I(d))} = S(I(d)).$$

Therefore, function I is the required positive solution of the IVP (4.1.3).

To show uniqueness, suppose I: $[0, \infty) \to [0, \infty)$ is a solution of the IVP (4.1.3) such that $I(d) > 0$ for all $d > 0$. Then $I(0) = 0$ and $I'(u) = S(I(u))$ for all $u > 0$. Equivalently,

$$\frac{I'(u)}{S(I(u))} = 1 \quad \text{for all} \quad u > 0.$$

Integrating this equation over $[0, d]$ and using the Fundamental Theorem of Calculus and Equation (4.1.5), we find that $F(I(d)) = d$ for every $d \geq 0$. Therefore, $I = F^{-1}$. The proof is completed.

Remark 1. Denote $S(0) := \lim_{x \to 0+} S(x)$ assuming the limit exists. If $S(0) = 0$ and function S meets all the assumptions of Theorem 4.1 then, along with a positive solution I, Equation (4.1.3) also has the trivial solution $I_0 = 0$. Furthermore, for every $d_0 > 0$, these two solutions can be combined into a new solution, I_1, by setting $I_1(d) = 0$ for $0 \le d \le d_0$ and $I_1(d) = I(d\text{-}d_0)$ for $d > d_0$.

Remark 2. One convenient class of ESFs that satisfy the conditions of Theorem 4.1 and produce a unique solution of the IVP (4.1.3) are continuous functions on $(0, \infty)$ that are uniformly bounded above and below by positive constants. Another class of ESFs with this property is the set of continuous positive functions S on $[0, \infty)$ such that $S(x) \le Cx^{\beta}$ with some constants $C > 0$ and $\beta \le 1$ for all sufficiently large $x > 0$.

Remark 3. Notice that apart from the assumed continuity, Theorem 4.1 does not require any additional smoothness of function S including commonly presumed Lipschitz condition or a stronger condition of the existence of a uniformly bounded derivative.

Remark 4. Theorem 4.1 has an immediate extension to the case where for some finite number $h > 0$, ESF S: $(0, h) \to (0, \infty)$ is a continuous function such that $\int_0^x \frac{du}{S(u)} < \infty$ for all $x \in (0, h)$ and $\int_0^h \frac{du}{S(u)} = \infty$. In this case, the unique positive solution I of the IVP (4.1.3) takes values in $[0, h)$ rather than $[0, \infty)$. If S is a 1-agent ESF, then its DER E has the range $[0, h)$.

Remark 5. If $m = \int_0^\infty \frac{du}{S(u)} < \infty$ (or $m = \int_0^h \frac{du}{S(u)} < \infty$, see Remark 4), then the positive solution, I, of the IVP (4.1.3) provided by Theorem 4.1 is only defined on the interval $[0, m)$ and $\lim_{d \to m-} I(d) = \infty$. If S is a 1-agent ESF, the interpretation of this possibility is that a finite dose, m, of the agent brings about a catastrophic endpoint effect.

Remark 6. Suppose S: $[0, \infty) \to [0, \infty)$ with $S(0) = 0$ is a continuous function such that $S(x) > 0$ for $x > 0$. It follows from the proof of Theorem 4.1 that if $\int_0^x \frac{du}{S(u)} = \infty$ for all $x > 0$, then the IVP (4.1.3) has only trivial solution.

Remark 7. Theorem 4.1 and all the above remarks remain true if function S: $(0, \infty) \to (0, \infty)$ is *piecewise continuous* with only finitely many jump discontinuities on any finite interval $(0, A)$. In this case, equality $I'(d) = S(I(d))$ is assumed to be true for all $d > 0$ such that $I(d)$ is a point of continuity of function S. EDRs with piecewise continuous ESFs are used below in Examples 6 and 9.

We now illustrate Theorem 4.1 with the following three examples of single-agent DERs.

1. Suppose $E(d) = d^a$, $a > 0$, then Equation (4.1.2) becomes $I' = aI^{1-1/a}$, $I(0) = 0$. Clearly, function $S(u) = au^{1-1/a}$ satisfies all the conditions of Theorem 4.1. Therefore, $I(d) = d^a$ is the only positive solution of Equation (4.1.3). However, for $a > 1$, this equation also has the extraneous trivial solution $I = 0$.
2. Consider the "extremely flat at $d = 0$" DER $E(d) = \exp(-d^{-a})$ with $a > 0$ and range $[0, 1)$ that produces the IVP $I' = aI\,[\ln(1/I)]^{1+1/a}$, $I(0) = 0$. In this case, the ESF $S(u) = au\,[\ln(1/u)]^{1+1/a}$ is defined for $0 < u < 1$ and satisfies the conditions of Remark 4 with $h = 1$. Thus, $I = E(d)$ is the only positive solution of the IVP (4.1.3). However, for any $a > 0$, it also has the trivial solution $I = 0$.
3. Let $E(d) = d/(d + 1)$ with range $[0, 1)$ be a Hill function, then $S(u) = (1\text{-}u)^2$, $0 \le u < 1$. Here again, the ESF satisfies the conditions of Remark 4 with $h = 1$. However, in this case, $I = 0$ is not a solution of the IVP (4.1.3), and so the given DER is the unique solution of this IVP.

4.2 | Applications of Theorem 4.1 to HIEA theory

Observe that the general premises (a)–(c) of the HIEA theory, see Section 3.1, can equivalently be expressed in terms of ESFs as assumptions of Theorem 4.1 or its extensions given in Remark 4 (in the case of finite h) and/or Remark 7 (for piecewise continuous ESFs).

We now address Equation (3.2.1) for the combination DER of N agents, which can alternatively be represented in the EDR form, see Equation (3.3.2), or as Equation (4.1.3) with a continuous (or piecewise continuous) combination ESF S given by Equation (4.1.4). The EDR HIEA equation has a formal solution $F(I)$ given by formula (3.3.3). Whether function F actually represents a solution to the IEA Equation (3.3.2) depends, therefore, on whether conditions (a) and (b) of Theorem 4.1 (or Remark 4) are satisfied. We begin with condition (a), that is, that $F(I)$ is finite or all $I > 0$. Note that in the case where $F_j'(0) = \infty$ (or equivalently if $E_j'(0) = 0$) for $j = 1, 2, \ldots, N$, the Riemann integral in Equation (3.3.3) should be treated as improper.

Proposition 4.2.1. *Suppose individual DERs satisfy assumptions (a)–(c). Then* $F(I) < \infty$ *for all* $I \in (0, h)$.

Proof. For a vector $\boldsymbol{x} = (x_1, x_2, \ldots, x_N)$ with positive components, non-zero number a and normalized positive weight sequence $\boldsymbol{r} = (r_1, r_2, \ldots, r_N)$ as above, denote by $A_a(\boldsymbol{x}, \boldsymbol{r})$ the weighted average of $\boldsymbol{x}$ of order a defined by

$$A_a(\boldsymbol{x},\boldsymbol{r}) = \left(\sum_{j=1}^{N} r_j x_j^a\right)^{1/a}. \tag{4.2.1}$$

Recall that for any fixed vectors $\boldsymbol{x}$ and $\boldsymbol{r}$, $A_a(\boldsymbol{x}, \boldsymbol{r})$ is an increasing function of a [30]. In particular, setting $a = -1$ and $a = 1$, we have $H(\boldsymbol{x}, \boldsymbol{r}) = A_{-1}(\boldsymbol{x}, \boldsymbol{r}) \le A_1(\boldsymbol{x}, \boldsymbol{r})$, which represents the inequality between the weighted harmonic and arithmetic means.

Fix $I \in (0, h)$. Applying the inequality between the two means to vector $\boldsymbol{x} = (F_1'(x), F_2'(x), \ldots, F_N'(x))$ and using Equation (3.3.2) and assumptions (b) and (c) from Section 3.1, we find that

$$F'(x) = \left[\sum_{j=1}^{N} \frac{r_j}{F_j'(x)}\right]^{-1} \le \sum_{j=1}^{N} r_j F_j'(x) \tag{4.2.2}$$

for all $x \in (0, I)$ with potentially finitely many exceptions. For any $\varepsilon \in (0, I)$, we integrate this inequality and use assumptions (a)–(c) from Section 3.1 to obtain

$$\int_\varepsilon^I \left[\sum_{j=1}^{N} \frac{r_j}{F_j'(x)}\right]^{-1} dx \le \int_\varepsilon^I \sum_{j=1}^{N} r_j F_j'(x) dx = \sum_{j=1}^{N} r_j \left[F_j(I) - F_j(\varepsilon)\right] \le \sum_{j=1}^{N} r_j F_j(I).$$

Therefore, from Equation (3.3.3), we infer that

$$F(I) = \lim_{\varepsilon \to 0} \int_\varepsilon^I \left[\sum_{j=1}^{N} \frac{r_j}{F_j'(x)}\right]^{-1} dx \le \sum_{j=1}^{N} r_j F_j(I) < \infty. \tag{4.2.3}$$

The proof is completed.

We now turn to a fundamental, yet more subtle, question regarding the validity of condition (b) of Theorem 4.1, that is, whether

$$F(\infty) = \int_0^\infty \left[\sum_{j=1}^{N} \frac{r_j}{F_j'(x)}\right]^{-1} \mathrm{d}x = \infty. \tag{4.2.4}$$

The following example demonstrates that even under the assumptions (a)–(c) of the HIEA theory, this does not necessarily have to be the case.

Example 1. Let functions $f, g: [0, \infty) \to (0, 1]$ be defined by $f(x) = 1/(1 + x)$ and $g(x) = 1/(1 + x)^2$. Partition their domain $[0, \infty)$ into intervals $[n, n + 1)$ for integer $n \ge 0$. Let A_n be such an interval for even n and B_n for odd n. Let $F_1'(x) = f(x)$ for $x \in A_n$ and $F_1'(x) = g(x)$ for $x \in B_n$; symmetrically, let $F_2'(x) = g(x)$ for $x \in A_n$ and

$F_2'(x) = f(x)$ for $x \in B_n$. Thus, the ESFs of two agents with EDRs $F_i(I) = \int_0^I F_i'(x)dx$, $i = 1, 2$, are switching between $1 + x$ and $(1 + x)^2$ on intervals A_n and B_n. Note that the functions F_1' and F_2' are positive and piece-wise continuous with finitely many jump discontinuities on any finite interval. We have

$$F_1(\infty) = \sum_{n=0}^{\infty} \int_{2n}^{2n+1} \frac{dx}{1+x} + \sum_{n=0}^{\infty} \int_{2n+1}^{2n+2} \frac{dx}{(1+x)^2} = \sum_{n=0}^{\infty} \ln\left(1 + \frac{1}{2n+1}\right) + \sum_{n=0}^{\infty} \frac{1}{(2n+2)(2n+3)} = \infty$$

because the first series diverges and the second converges. Similarly, $F_2(\infty) = \infty$. Therefore, functions F_1 and F_2 satisfy conditions (a)–(c) of the HIEA theory with $h = \infty$, and so their inverse functions can serve as legitimate DERs for the two agents. We now show that the DER of the 1:1 combination of these agents "blows up" at some finite dose. According to Remark 5 to Theorem 4.1 and Equation (4.2.4), we only have to verify that

$$\int_0^{\infty} \frac{2}{[F_1'(x)]^{-1} + [F_2'(x)]^{-1}} dx < \infty.$$

In fact,

$$\int_0^{\infty} \frac{2}{[F_1'(x)]^{-1} + [F_2'(x)]^{-1}} dx = \int_0^{\infty} \frac{2}{[f(x)]^{-1} + [g(x)]^{-1}} dx = \int_0^{\infty} \frac{2}{(1+x)(2+x)} dx = 2\ln 2.$$

Therefore, for the combination DER, E, we have $\lim_{d \to 2\ln 2-} E(d) = \infty$.

Example 1 demonstrates that indiscriminate use of 1-agent DERs may occasionally lead to the biologically impossible "blow-up" effect where in the absence of synergy and antagonism in the sense of HIEA synergy theory, a combination of several "regular" DERs (i.e., with finite effect for any finite dose) may prove "singular," that is, produce infinite effect at finite dose. To avoid the "blow-up" phenomenon, individual EDRs must satisfy the condition

$$F(h) = \int_0^h \left[\sum_{j=1}^N \frac{r_j}{F_j'(x)}\right]^{-1} dx = \infty, \tag{4.2.5}$$

compared with Equation (4.2.4), or equivalently, when expressed through individual ESFs,

$$\int_0^h \frac{dx}{\sum_{j=1}^N r_j S_j(x)} = \infty.$$

Interestingly, the "no blow-up" condition (4.2.5) can be restated in an equivalent form that only contains individual EDRs but is free of their weights:

Proposition 4.2.2. *Condition (4.2.5) is equivalent to*

$$\int_0^h \min_{1 \le j \le N} F_j'(x) dx = \infty. \tag{4.2.6}$$

Proof. Consider the following estimates for the combination ESF $S = \sum_{j=1}^N r_j S_j$:

$$r(x) \max_{1 \le j \le N} S_j(x) \le S(x) \le \max_{1 \le j \le N} S_j(x), 0 < x < h, \tag{4.2.7}$$

where $r(x)$ is the sum of weights r_i over all indices i such that $S_i(x) = \max_{1 \le j \le N} S_j(x)$. Applying Equation (4.1.2) to the combination and individual EDRs and using the estimate $r(x) \ge \min_{1 \le j \le N} r_j =: \rho > 0$, we represent inequalities (4.2.7) through EDRs in the form

$$\min_{1 \le j \le N} F_j'(x) \le F'(x) \le \rho^{-1} \min_{1 \le j \le N} F_j'(x), \quad 0 < x < h,$$

whence by integration we find that

$$\int_0^I \min_{1 \le j \le N} F_j'(x)dx \le F(I) \le \rho^{-1} \int_0^I \min_{1 \le j \le N} F_j'(x)dx, \quad 0 < I < h.$$

Passage to limit in these inequalities as $I \to h-$ yields

$$\int_0^h \min_{1 \le j \le N} F_j'(x)dx \le F(h) \le \rho^{-1} \int_0^h \min_{1 \le j \le N} F_j'(x)dx.$$

Therefore, $F(h) = \infty$ iff condition (4.2.6) is met, which completes the proof.

Remark 1. In terms of ESFs, Equation (4.2.6) takes on the following equivalent form:

$$\int_0^h \frac{dx}{\max\limits_{1 \le j \le N} S_j(x)} = \infty.$$

Remark 2. Suppose kth agent is strongly dominant, that is, $\min\limits_{1 \le j \le N} F_j'(x) = F_k'(x)$ for all $x \ge 0$. Then condition (4.2.6) is automatically satisfied. Thus, in the presence of a strongly dominant agent, no "blow-up" can occur.

We conclude this section with an example illustrating Theorem 4.1.

Example 2. Consider a 1:1 combination ($r_1 = r_2 = 0.5$) of two agents with DERs $E_1(d) = d^2$ and $E_2(d) = d^3$. In this case, $h = \infty$, $F_1(I) = I^{1/2}$, $F_2(I) = I^{1/3}$, $S_1(I) = 2I^{1/2}$, and $S_2(I) = 3I^{2/3}$. From Equation (3.3.3),

$$F(I) = 2\int_0^I \frac{dx}{2x^{1/2} + 3x^{2/3}}, \quad I \ge 0.$$

Clearly, the singularity of the integrand at $x = 0$ is integrable, and the "no blow-up" condition (4.2.4) is satisfied so that the combination ESF meets all conditions of Theorem 4.1. By a rationalizing substitution $x = t^6$, we find that

$$F(I) = 12\int_0^{I^{1/6}} \frac{t^2 dt}{3t + 2} = 2I^{\frac{1}{3}} - \frac{8}{3}I^{\frac{1}{6}} + \frac{16}{9}\ln\left(1 + 1.5I^{\frac{1}{6}}\right). \tag{4.2.8}$$

The 1-agent EDRs and the combination EDR $F(I)$ are shown graphically in Figure 4. Note that while combination EDR $F(I)$ is computable in closed form, this is not so for its inverse function, $E(d)$.

5 | MATHEMATICAL PROPERTIES OF HIEA SYNERGY THEORY: RESULTS, EXAMPLES, AND COUNTEREXAMPLES

In Sections 5.1 and 5.2, we assume that all 1-agent DERs have the same range. Section 5.3 deals with a more general case where some of the ranges may be distinct and with complications that then arise.

5.1 | Similarity theory

The classic similarity theory, see, for example, Berenbaum [1], posits that 1-agent DERs are obtained by scaling of the same DER:

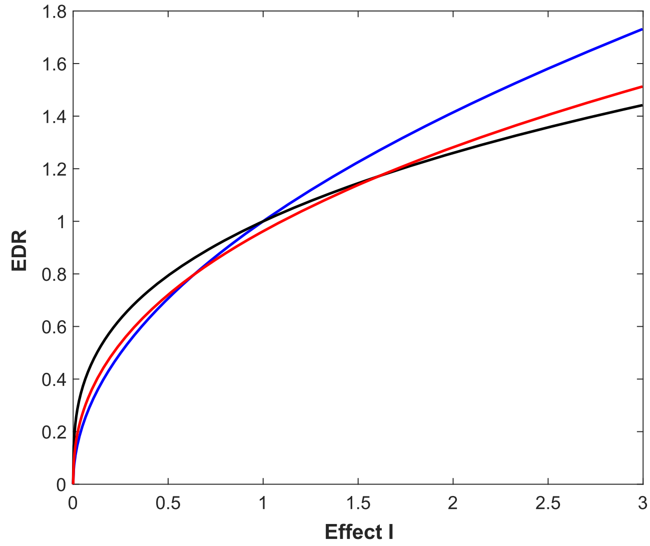

FIGURE 4 EDR plot for quadratic and cubic DERs. The two mixture components, contributing equal doses, have EDRs $F_1(I) = I^{1/2}$ (blue curve) and $F_2(I) = I^{1/3}$ (black curve). The mixture NSNA HIEA EDR, see Equation (4.2.8), is represented by the red curve. A combination (effect, dose) pair below the red curve would indicate less dose than expected from experiments with the two components acting individually, that is, synergy. Above the red curve is the antagonism region. [Colour figure can be viewed at wileyonlinelibrary.com]

$$E_j(d) = \varphi(C_j d), \quad 1 \leq j \leq N, \tag{5.1.1}$$

where function φ: $[0, \infty) \to [0, h)$ is assumed to have properties (a)–(c) postulated in Section 3.1 and C_j, $1 \leq j \leq N$, are positive coefficients. Let ψ: $[0, h) \to [0, \infty)$ be the inverse function for φ. Then for the 1-agent EDRs, we have $F_j(I) = C_j^{-1}\psi(I)$, $0 \leq I < h$. This is interpreted by saying that different agents have constant potency ratios: $F_j(I)/F_i(I) = C_i/C_j$ for all $I > 0$. Equation (3.3.3) leads to the following expression for the NSNA combination EDR:

$$F(I) = \int_0^I \left[\sum_{j=1}^N \frac{r_j C_j}{\psi'(x)}\right]^{-1} dx = \left(\sum_{j=1}^N r_j C_j\right)^{-1} \psi(I). \tag{5.1.2}$$

Then the combination NSNA HIEA DER,

$$I(d) = \varphi\left[\left(\sum_{j=1}^N r_j C_j\right) d\right], \tag{5.1.3}$$

has the same form as 1-agent DERs, see Equation (5.1.1), and is sandwiched between respective individual DERs with the smallest and largest coefficients C_j. Another consequence that can be drawn from Equation (5.1.3) is that similar DERs give rise to linear isoboles.

It follows from Equation (5.1.2) that

$$\frac{1}{F(I)} = \sum_{j=1}^N \frac{r_j C_j}{\psi(I)} = \sum_{j=1}^N \frac{r_j}{F_j(I)},$$

that is, LBA criterion, see Equation (2.3), is satisfied. Conversely, by a similar argument, LBA implies HIEA. Thus, within the classic similarity theory, HIEA and LBA synergy theories are equivalent.

Consider now a more general case where individual DERs are obtained by double scaling from the same DER, that is,

$$E_j(d) = P_j \varphi(C_j d), \; 1 \leq j \leq N, \tag{5.1.4}$$

where (P_j, C_j) are pairs of positive coefficients. In view of Equation (3.3.3), the NSNA HIEA EDR for the combined action of N agents is given by

$$F(I) = \int_0^I \left[\sum_{j=1}^N \frac{r_j P_j C_j}{\psi'\left(P_j^{-1} x\right)} \right]^{-1} dx. \tag{5.1.5}$$

Discussed below are some instances where this integral can be computed in closed form.

Case 1. $\varphi(d) = d^a$, where $a > 0$.

In this case $\psi(I) = I^{1/a}$, and from Equation (5.1.5), we find that

$$F(I) = \int_0^I \left[\sum_{j=1}^N \frac{a r_j P_j C_j}{\left(P_j^{-1} x\right)^{\frac{1}{a}-1}} \right]^{-1} dx = [A(a)]^{-1/a} \int_0^I a^{-1} x^{1/a-1} dx = [A(a)]^{-1/a} I^{1/a},$$

where

$$A(a) = \left(\sum_{j=1}^N r_j P_j^{1/a} C_j \right)^a$$

is the weighted average of order $1/a$ of the vector $(P_1 C_1^a, P_2 C_2^a \ldots, P_N C_N^a)$; see Equation (4.2.1). Therefore, the combination NSNA DER is given by the formula

$$E(d) = A(a) d^a = \varphi\left[\left(\sum_{j=1}^N r_j P_j^{\frac{1}{a}} C_j \right) d \right]$$

that is, is of the same kind as individual DERs, compare with Equation (5.1.3).

Case 2.

$$\varphi(d) = \ln(d+1).$$

Then $\psi(I) = \exp(I)$-1, and in view of Equation (5.1.5)

$$F(I) = \int_0^I \left(\sum_{j=1}^N r_j P_j C_j e^{-x/P_j} \right)^{-1} dx.$$

This integral can be computed explicitly only in a few particular instances. One of them occurs when $N = 2$ and one of the coefficients P_1, P_2 is twice as large as the other. Suppose $P_2 = P$ and $P_1 = 2P$, then by a change of variable $u = \exp\{x/2P\}$, we have

$$F(I) = \frac{1}{P} \int_0^I \left[2 r_1 C_1 e^{-x/2P} + r_2 C_2 e^{-x/P} \right]^{-1} dx = \frac{1}{P} \int_0^I \frac{e^{x/P} dx}{2 r_1 C_1 e^{x/2P} + r_2 C_2}$$
$$= 2 \int_1^{e^{I/(2P)}} \frac{u du}{2 r_1 C_1 u + r_2 C_2} = \frac{1}{r_1 C_1} \left[e^{I/2P} - 1 - \frac{r_2 C_2}{2 r_1 C_1} ln\left(1 + \frac{2 r_1 C_1}{2 r_1 C_1 + r_2 C_2} \left(e^{I/2P} - 1 \right) \right) \right].$$

Here, yet again, the combination EDR is, while the combination DER is not, computable in closed form.

In particular, Case 2 leads to the following specific example:

Example 3. Set $N = 2$, $r_1 = r_2 = 0.5$ and $P = C_1 = C_2 = 1$, then

$$F(I) = 2\left(e^{I/2} - 1\right) - \ln\left(1 + \frac{2}{3}\left(e^{\frac{I}{2}} - 1\right)\right). \tag{5.1.6}$$

The graphs of the individual EDRs $F_1(\mathrm{I}) = \exp(I/2)$-1, $F_2(I) = \exp(I)$-1, and the combination EDR $F(I)$ are shown in Figure 5.

5.2 | The betweenness property for HIEA synergy theory

In this section, we study the betweenness property for HIEA and discover a surprising asymmetry between the upper and lower bounds for the combination EDR. Because betweenness violation by the NSNA HIEA EDR curve is a newly discovered, important flaw of HIEA synergy theory, we set out to delineate specifically when violation occurs and what conditions on 1-agent DERs or EDRs ensure betweenness. Assumptions (a)–(c) of Section 3.1 remain a general premise for all the results in this section.

Proposition 5.2.1. *The N-agent combination HIEA EDR F(I) satisfies the inequality*

$$F(I) \leq max\left\{F_j(I) : 1 \leq \mathrm{j} \leq N\right\},\ 0 \leq I < h. \tag{5.2.1}$$

Proof. This inequality immediately follows from inequality (4.2.3).

Thus, under the NSNA condition, the combination EDR curve cannot cross into the region above the upper envelope of individual EDR curves. Equivalently,

$$E(d) \geq \min\left\{E_j(d) : 1 \leq \mathrm{j} \leq N\right\},\ d \geq 0.$$

A natural question is whether an inequality dual to (5.2.1) holds for the lower envelope of individual EDR curves. Example 2 in Section 4.2 gives a negative answer to this question; see Figure 4. In fact, the two individual EDR curves in Example 2 intersect at point (1, 1) while for the combination EDR

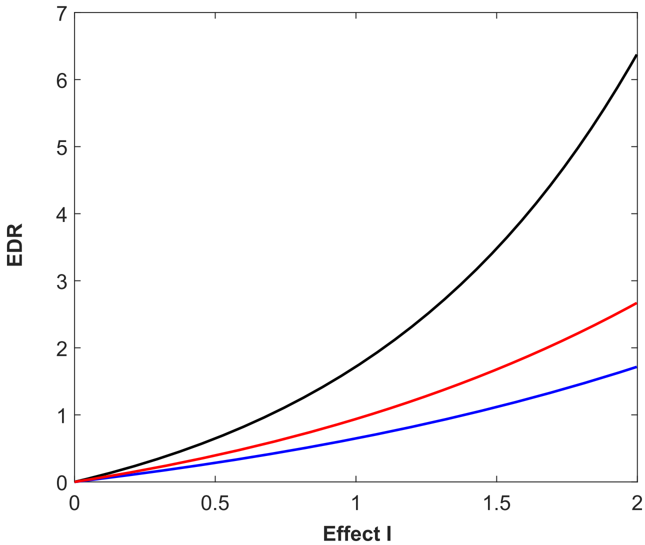

FIGURE 5 EDR plot illustrating the betweenness property in similarity theory. $F_1(I) = \exp(I/2)$-1 (blue curve) and $F_2(I) = \exp(I)$-1 (black curve) are EDRs of two equally contributing agents. The combination EDR $F(I)$ is given in Equation (5.1.6) and represented by the red curve. Note that, as in Case 1 discussed in Section 5.1, the combination EDR stays between the lower and upper individual EDR curves, that is, has the betweenness property. Therefore, the same also holds for the DERs. [Colour figure can be viewed at wileyonlinelibrary.com]

$$F(1) = \frac{16}{9} \ln 2.5 - \frac{2}{3} \cong 0.962 < 1.$$

In Example 2, both agents had infinite range of effects. To make sure this is inessential for betweenness violation, we offer the following additional example.

Example 4. Consider a 1:1 combination of two agents with Hill DERs $E_1(d) = d/(d + 1)$ and $E_2(d) = d^2/(d^2 + 2)$. In this case, $h = 1$ and $F_1(I) = I/(1\text{-}I)$, $F_2(I) = [2I/(1\text{-}I)]^{1/2}$, $S_1(I) = (1\text{-}I)^2$, $S_2(I) = (1\text{-}I)[2I(1\text{-}I)]^{1/2}$, $0 \leq I < 1$. From Equation (3.3.3), we obtain

$$F(I) = 2\int_0^I \frac{dx}{(1-x)\left[1-x+\sqrt{2x(1-x)}\right]},\ 0 \leq I < 1.$$

Note that the lower envelope of the two individual EDRs must pass through the point (2/3, 2) of their intersection. However, numerical integration yields $F(2/3) \cong 1.8028 < 2$, thus indicating violation of the betweenness property; see Figure 6.

Examination of Examples 2 and 4 leads to the following questions, which, to avoid duplication, we pose for EDRs:

(1) When does the combination EDR stay above the lower envelope of individual EDRs?
(2) Is it true that in the case $h = \infty$ the combination EDR curve eventually (i.e., for sufficiently large effects) enters the region between the lower and upper envelopes of individual EDRs?
(3) When does the combination EDR curve for two agents pass through the intersection point of their individual EDRs?

The following statement provides a simple sufficient condition for the affirmative answer to question 1 in the case of two agents.

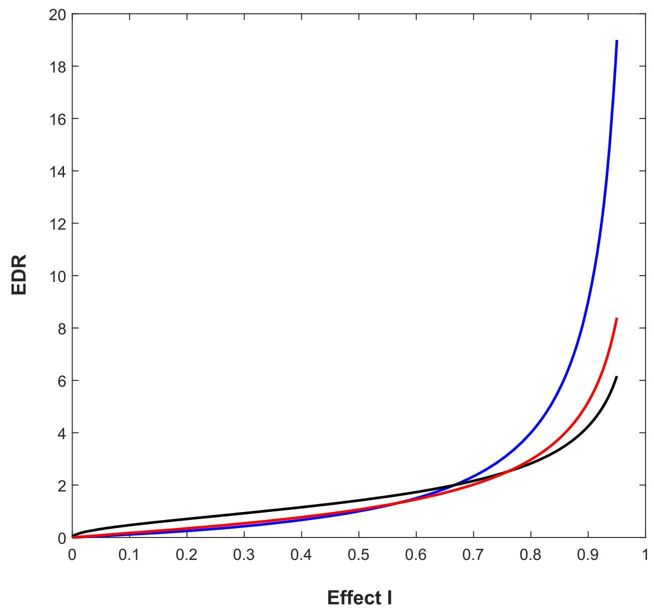

FIGURE 6 EDR plot illustrating the lack of betweenness for Hill DERs with identical ranges of effect. 1-agent EDRs are $F_1(I) = I/(1\text{-}I)$ (blue curve) and $F_2(I) = [2I/(1\text{-}I)]^{1/2}$ (black curve) while the combination NSNA EDR is represented by red curve. Near (effect, dose) point (2/3, 2), there is a two-dimensional area above the red curve but below both the blue and the black curves that lies in the antagonism region of the figure. This betweenness violation contradicts the intuitive notion that a combination dose more effective than any 1-agent dose must be in the synergy region of the effect-dose plane. For more details, see Example 4 in Section 5.2. [Colour figure can be viewed at wileyonlinelibrary.com]

Proposition 5.2.2. *Suppose $N = 2$ and one of the two agents, say agent 1, is strongly dominant, that is,* $F_1'(\mathrm{I}) \le F_2'(\mathrm{I})$ for $0 < \mathrm{I} < \mathrm{h}$. Then for the *combination* HIEA EDR F(I), we have

$$F_1(I) \le F(I) \le F_2(I) \text{ for all } I \in [0,h). \tag{5.2.2}$$

Proof. It follows from Equation (3.3.2) and inequalities (2.1) that under the assumptions of this Proposition $F_1'(I) \le F'(I) \le F_2'(I)$ for $0 < I < h$, which after integration yields inequalities (5.2.2), as required.

According to Equation (4.1.2), universal (i.e., valid for all effects $I \in (0,h)$) ordering of the derivatives of EDRs assumed in Proposition 5.2.2 is equivalent to universal reverse ordering of the agents' ESFs. Thus, in the case $N=2$, universal ordering of the agents' ESFs entails the betweenness property.

An immediate generalization of the betweenness property for combination EDR expressed by Equation (5.2.2) to any number of agents is as follows:

Proposition 5.2.3. *Suppose that for some k, $1 \le k \le N$, kth agent is strongly dominant, that is, the derivatives of EDRs F_j, $1 \le j \le N$, $j \ne k$, satisfy the inequality* $F_j'(\mathrm{I}) \ge F_k'(\mathrm{I})$ for all $\mathrm{I} \in$ *[0, h). Then the combination HIEA EDR has the betweenness property.*

Proof. From the assumed inequality for the derivatives of EDRs, we conclude by integration that $F_j \ge F_k$ on *[0, h)* for all $j \ne k$. Therefore, $min\{F_{\mathrm{j}}: 1 \le \mathrm{j} \le N\} = F_{\mathrm{k}}$. Using Equations (3.3.2) and (2.1), we find that $F' \ge F_k'$ on *[0, h)*, which implies through integration that $F \ge F_k = min\{F_{\mathrm{j}}: 1 \le j \le N\}$. Combining this with Equation (5.2.1) establishes the required betweenness property.

Remark. A slight modification of the proof of Proposition 4.2.2 would show that if kth agent is strongly dominant then

$$F_k(I) \le F(I) \le {r_k}^{-1} F_k(I), \quad 0 \le I < h.$$

Thus, a dominant agent imposes robust lower and upper bounds on the combination EDR that are independent of the number, weights, and EDRs of other agents as long as the kth agent remains dominant and retains its weight r_k.

We show now that, barring an unlikely special case, the combination EDR always passes below any intersection point of two 1-agent EDRs, as was illustrated by Figures 4 and 6.

Proposition 5.2.4. *Suppose $N = 2$ and $A := F_1(I^*) = F_2(I^*)$ for some $I^* > 0$. If the combination EDR F(I) has the property that $F(I^*) = A$ then $F_1(I) = F_2(I)$ for all $I \in [0, I^*]$.*

Proof. Using Equation (4.2.2), which is based on the inequality between weighted harmonic and arithmetic means, we find that

$$A = F(I*) = \int_0^{I^*} F'(x)dx \le \int_0^{I^*} \left[r_1 F_1'(x) + r_2 F_2'(x)\right] dx = r_1 F_1(I^*) + r_1 F_2(I^*) = A. \tag{5.2.3}$$

Thus, the inequality in Equation (5.2.3) turns into equality. This implies, due to the piecewise continuity of functions F_1' and F_2', that inequality (4.2.2) is actually an equality for all $\mathrm{x} \in (0, I^*]$, except possibly for finitely many points. Recall that the inequality between weighted means of two different orders of a vector with positive components turns into equality if and only if all the components of the vector are identical [30]. Therefore, $F_1'(x) = F_2'(x)$ for all $x \in (0, I^*]$ except possibly for finitely many points. Then by integration, we find that $F_1(I) = F_2(I)$ for all $I \in [0, I^*]$, as required.

We illustrate Proposition 5.2.2 with LQ DERs. Recall that LQ DER has the form $E(d) = \alpha d + \beta d^{\,2}$, where $\alpha, \beta \ge 0$ and $\alpha + \beta > 0$. For the corresponding EDR and its derivative, we have

$$F(I) = \frac{2I}{\alpha + \sqrt{\alpha^2 + 4\beta I}} \text{ and } F'(I) = \frac{1}{\sqrt{\alpha^2 + 4\beta I}}.$$

Therefore, if $E_i(d) = \alpha_i d + \beta_i d^{\ 2}$, $i = 1, 2$, are two distinct LQ DER such that $\alpha_1 \le \alpha_2$ and $\beta_1 \le \beta_2$ then agent 2 is strongly dominant, which implies the betweenness property. Consider the following specific example.

Example 5a. Suppose $N = 2$, $r_1 = r_2 = 0.5$, $\alpha_1 = 1$, $\alpha_2 = 2$, $\beta_1 = 0.5$, and $\beta_2 = 2$. Then the combination EDR curve lies between the two individual EDRs; see Figure 7A.

If, on the contrary, $\alpha_1 < \alpha_2$ and $\beta_1 > \beta_2$, then the two 1-agent DER curves intersect at the dose point $d = (\alpha_2 - \alpha_1)/(\beta_1 - \beta_2)$. In this case, Proposition 5.2.4 implies that the betweenness property cannot hold, as illustrated by the following example.

Example 5b. Let $N = 2$, $r_1 = r_2 = 0.5$, $\alpha_1 = 1$, $\alpha_2 = 5$, $\beta_1 = 4$, and $\beta_2 = 1$. In this case, the combination EDR curve passes below the point of intersection of the two individual EDR curves; see Figure 7B.

Although the combination EDR for any two LQ DERs can be computed in closed form, the formula is fairly cumbersome; that is why the combination EDR curves in Figure 7 were generated using numerical integration.

Proposition 5.2.3 states that the presence of a strongly dominant agent implies the betweenness property. Is the same true under a weaker dominance condition? A negative answer to this question, as well as to the above question 2 about eventual betweenness, is provided by the following example.

Example 6. Let $N = 2$, $r_1 = r_2 = 0.5$, $h = \infty$, $F_1(I) = I$, and $F_2(I)$ is a piecewise linear function such that $F_2'(I) = 0.2$ for $0 \le I < 1$, $F_2'(I) = 5$ for $1 \le I < 1.1$, and $F_2'(I) = 1$ for $I \ge 1.1$. Then

$$F_2(I) = \begin{cases} I/5 & \text{for } 0 \le I < 1 \\ 5I - 4.8 & \text{for } 1 \le I < 1.1 \\ I - 0.4 & \text{for } I \ge 1.1 \end{cases} \tag{5.2.4}$$

A simple computation based on Equation (3.3.3) yields

$$F(I) = \begin{cases} I/3 & \text{for } 0 \le I < 1 \\ 5I/3 - 4/3 & \text{for } 1 \le I < 1.1 \,. \\ I - 0.6 & \text{for } I \ge 1.1 \end{cases}$$

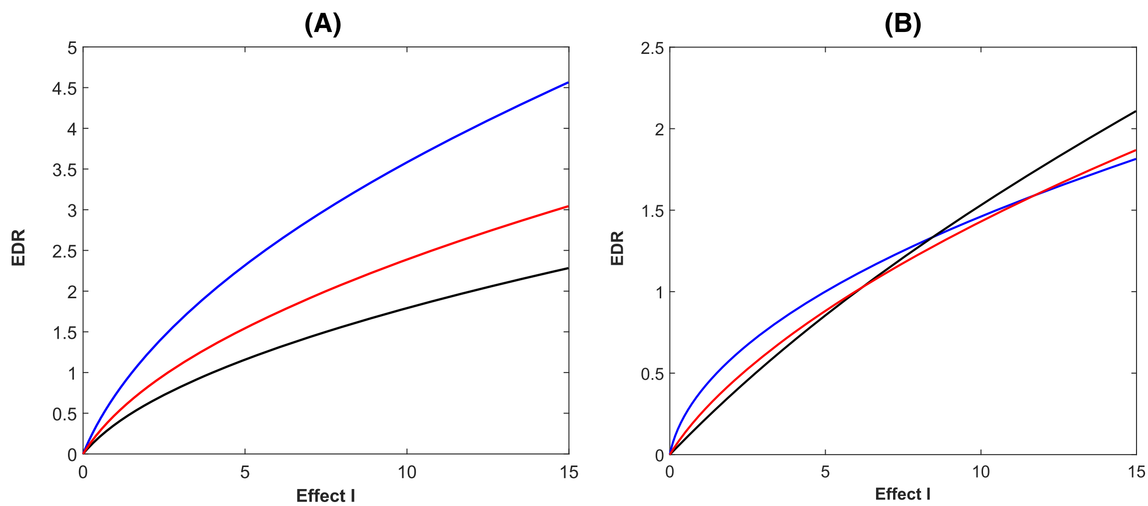

FIGURE 7 (A) Combination EDR for LQ DERs of two agents with one strongly dominating the other. 1-agent LQ DERs are $E_1(d) = 2d + 2d^2$ (blue EDR curve) and $E_2(d) = d + 0.5d^2$ (black EDR curve). The combination EDR is shown as the red curve. Note the betweenness property. (B) Combination EDR for two intersecting 1-agent LQ DERs. 1-agent LQ DERs are $E_1(d) = 5d + d^2$ (blue EDR curve) and $E_2(d) = d + 4d^2$ (black EDR curve). The combination EDR is shown as the red curve. The betweenness property is violated near the intersection point. [Colour figure can be viewed at wileyonlinelibrary.com]

In this case, see Figure 8, $F_2(\mathrm{I}) < F_1(\mathrm{I})$ for all $I > 0$, and the combination NSNA EDR curve stays below *both* 1-agent EDRs for all $I > 1.04$.

5.3 | HIEA synergy theory for agents with distinct ranges of effect

Our aim in this section is to extend HIEA theory to the case where the ranges of effect of $N \geq 2$ agents are not all identical. The idea of such extension was formulated by Hand [8]. Suppose $h_1 < h_2 < \ldots < h_M$, where $2 \leq M \leq N$ and h_M can be finite or infinite, are the agents' distinct maximum effects. Consider all the agents with the range of effect $[0, h_1)$. Renumbering these agents, we may assume these to be agents 1 through n_1, where $n_1 \geq 1$. Then $\lim_{d\to\infty} E_j(d) = h_1 < \infty$ for $1 \leq j \leq n_1$. This means that even arbitrarily large doses of any such agent, for example, agent 1, cannot produce effects $\geq h_1$. Thus, the first n_1 terms in the basic HIEA Equation (3.2.1) must vanish for $I \geq h_1$ or, in other words, for such combination effects I, the first n_1 terms must be dropped from Equation (3.2.1). Similarly, for $I \geq h_2$, all the additional terms in Equation (3.2.1) corresponding to the agents whose range of effect is $[0, h_2)$ must be dropped from Equation (3.2.1). By renumbering these agents, we may assume that these are agents $n_1 + 1$ through n_2, where $n_1 < n_2 \leq N$, and so on. Eventually, only agents with the range of effect $[0, h_M)$ will remain in the HIEA equation. A parallel drop-off of terms will occur in Equation (3.3.2). The same reduction methodology can be applied to Equation (2.3) (and more generally, to Equation 1.3.2) that describe NSNA combination EDR under LBA synergy theory; see Lederer et al. and Sinzger et al. [3, 5].

To make the described equation reduction justified and compatible with assumptions (b) and (c) in Section 3.1, we need the following additional assumption:

$$(d)\ \textit{If jth agent}, 1 \leq j \leq N, \textit{has finite range of effect, then} \lim_{d\to\infty} E_j'(d) = 0.$$

Under this assumption, the drop-off of terms in the RHS of Equation (3.3.2) will not violate its continuity as a function of I.

Condition (d) is satisfied if $E_j'(d)$ is a decreasing function for all, or all sufficiently large, d. In particular, this is true for Hill DERs of the form $hd^a/(d^a + b)$ with $a, b, h > 0$, and $h\exp\{-d^{-a}\}$ with $a > 0$. On the other hand, it is easy to construct a positive continuous integrable function e on $[0, \infty)$ that does not vanish at ∞. The function $E(\mathrm{d}) = \int_0^d e(x)dx$ meets conditions (a)–(c) but fails to satisfy condition (d).

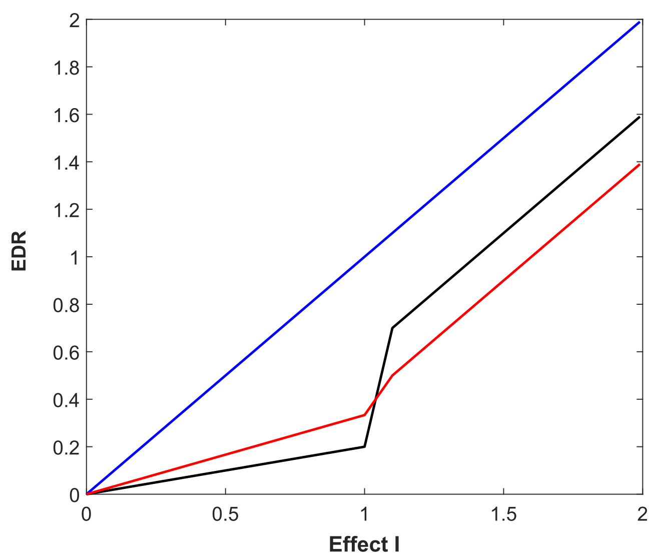

FIGURE 8 Counterexample to the eventual betweenness with piecewise linear EDRs of two agents, one dominating the other. The red piecewise linear combination EDR curve stays beneath the two linear (or piecewise linear) component EDR curves in the effect interval (1.04, ∞). One of the two agents is dominant. For more details, see Example 6 in Section 5.2. [Colour figure can be viewed at wileyonlinelibrary.com]

5.3.1 | Examples

Our first example deals with a 1:1 mixture of two agents, one with a finite range of effect, which by scaling can be assumed to be [0, 1), and the other with infinite range of effect. Suppose that $E_1(d) = d$ and $E_2(d) = d/(d + a^2)$ with $a > 0$. Note that the two DER curves intersect at some point $d \in (0, 1)$ iff $0 < a < 1$. For the corresponding EDRs, we have $F_1(I) = I$ and $F_2(I) = a^2 I/(1\text{-}I)$, so that $F_2'(I) = 1$ and $F_2'(I) = a^2/(1\text{-}I)^2$. From Equation (3.3.2), we find that

$$F'(I) = \begin{cases} \dfrac{2a^2}{(I-1)^2 + a^2} & for\, 0 \le I < 1 \\ 2 & for\, I \ge 1 \end{cases}$$

whence by integration, we obtain

$$F(I) = \begin{cases} 2a\left(\tan^{-1}\dfrac{1}{a} - \tan^{-1}\dfrac{1-I}{a}\right) & for\, 0 \le I < 1 \\ 2\left(I + a\tan^{-1}\dfrac{1}{a} - 1\right) & for\, I \ge 1 \end{cases}.$$

The values $a = \sqrt{3}$ and $a = 1/\sqrt{3}$ produce the following specific examples:

Example 7a. Let $a = \sqrt{3}$, in which case individual EDR and DER curves do not intersect. Here,

$$F(I) = \begin{cases} \dfrac{\pi}{\sqrt{3}} - 2\sqrt{3}\tan^{-1}\dfrac{1-I}{\sqrt{3}} & for\ 0 \le I < 1 \\ 2\left(I + \dfrac{\pi}{2\sqrt{3}} - 1\right) & for\, I \ge 1 \end{cases} \tag{5.3.1a}$$

and, in spite of two different ranges of effect, the combination EDR curve lies between the two 1-agent EDR curves on the interval [0, 1), see Figure 9A.

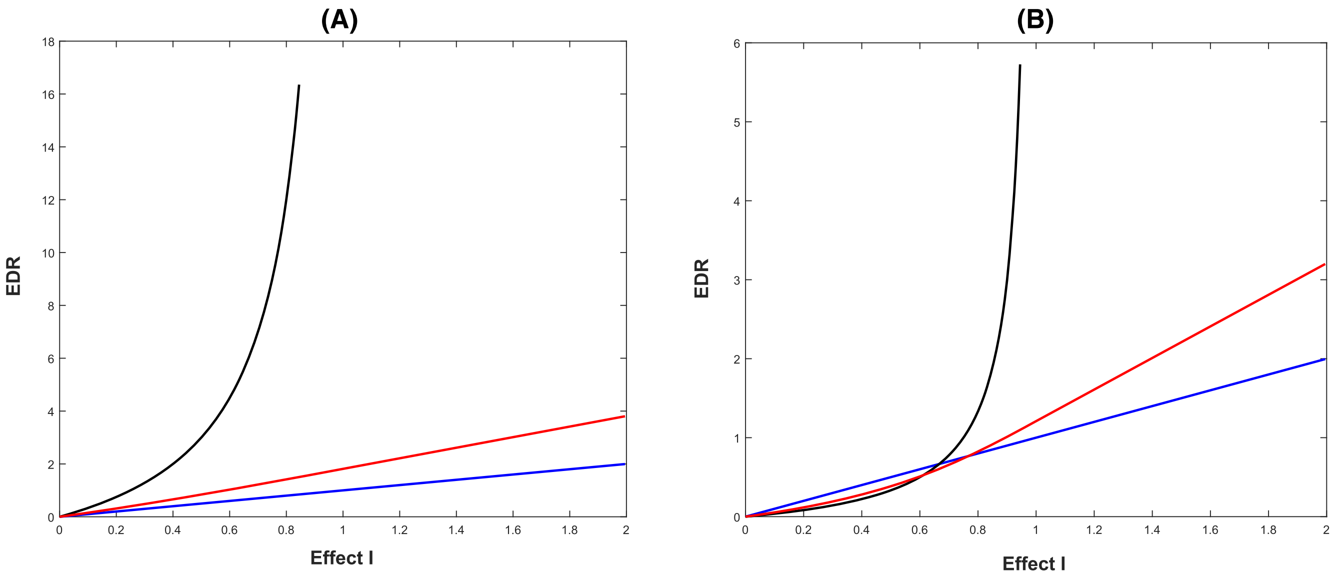

FIGURE 9 (A) Combination EDR for two non-intersecting DERs with distinct (one finite and one infinite) ranges of effect. Component EDRs are $F_1(I) = I$ (blue line) and $F_2(I) = 3I/(1\text{-}I)$ (black curve). The combination EDR (red curve) is given by Equation (5.3.1a). Notice the betweenness property. (B) Combination EDR for two intersecting DERs with distinct (one finite and one infinite) ranges of effect. Component EDRs are $F_1(I) = I$ (blue line) and $F_2(I) = I/[3(1\text{-}I)]$ (black curve). The combination EDR (red curve) is given by Equation (5.3.1b). A violation of betweenness occurs near the intersection point. [Colour figure can be viewed at wileyonlinelibrary.com]

Example 7b. Let $a = 1/\sqrt{3}$, in which case individual EDR and DER curves intersect at (2/3, 2/3). Here,

$$F(I) = \begin{cases} \frac{2}{\sqrt{3}}\left(\frac{\pi}{3} - \tan^{-1}\left[\sqrt{3}(1-I)\right]\right) & for\, 0 \le I < 1 \\ 2\left(I + \frac{\pi}{3\sqrt{3}} - 1\right) & for\, I \ge 1 \end{cases}. \tag{5.3.1b}$$

Because

$$F(2/3) = \frac{\pi}{3\sqrt{3}} \cong 0.605 < 2/3,$$

the combination EDR curve passes below the point of intersection of individual EDR curves thus violating the betweenness property, as shown in Figure 9B.

Our next example involves a 1:1 mixture of two agents whose DERs have distinct finite ranges of effect. Let $E_1(d) = d/(d+a)$ and $E_2(d) = 2d/(d+b)$ with a, $b > 0$ be two fractional linear Hill DERs. The two DER curves intersect at some $d > 0$ iff $b > 2a$, in which case $d = b\text{-}2a$. For the corresponding EDRs, we have $F_1(I) = aI/(1\text{-}I)$ and $F_2(I) = bI/(2\text{-}I)$. Using Equation (3.3.2), we find after some algebra that

$$F'(I) = \begin{cases} \frac{p}{(I-q)^2 + r^2} & for\ 0 \le I < 1 \\ \frac{4b}{(2-I)^2} & for\ 1 \le I < 2 \end{cases}$$

where

$$p = \frac{4ab}{a+2b},\ q = \frac{2(a+b)}{a+2b},\ r = \frac{\sqrt{2ab}}{a+2b}.$$

Then by integration, we obtain

$$F(I) = \begin{cases} 2\sqrt{2ab}\left[\tan^{-1}\frac{\sqrt{2}(a+b)}{\sqrt{ab}} - \tan^{-1}\frac{2(a+b)-(a+2b)I}{\sqrt{2ab}}\right] & for\ 0 \le I < 1 \\ 2\sqrt{2ab}\left[\tan^{-1}\frac{\sqrt{2}(a+b)}{\sqrt{ab}} - \tan^{-1}\sqrt{\frac{a}{2b}}\right] + 4b\frac{I-1}{2-I} & for\ 1 \le I < 2 \end{cases}. \tag{5.3.2}$$

Specialization of these formulas leads to the following two examples.

Example 8a. $a = b = 1$. Here, individual EDR curves do not intersect, and the combination EDR curve stays between them on the interval [0, 1); see Figure 10A. For another instance of non-intersecting fractional linear Hill DER curves, see example 3.4 in Hand [8].

Example 8b. $a = 1$, $b = 12$. In this case, individual EDR curves intersect at (10/11, 10), and the betweenness property is violated; see Figure 10B.

Examination of Figure 9B leads to the following question. Observe that for $I \ge 1$ (i.e., after the term in Equation 3.3.2 associated with agent 1 has been dropped), the combination EDR curve stays above the EDR curve for agent 2. Is this always true? In the case $N = 2$ if agent 1 is dropped from the IEA equation for $h_1 \le I < h_2$, the IEA equation on this interval of effects takes on the form $F'(I) = F_2'(I)/r_2$, which implies "eventual betweenness," that is, that the combination EDR curve will stay above the EDR curve for agent 2 for all sufficiently large I if $h_2 = \infty$ or for I sufficiently close to h_2 if the latter is finite. That the combination EDR curve doesn't have to always (i.e., not only "eventually") stay above the EDR curve for the remaining agent in the case of finite h_2 is demonstrated by Example 8b.

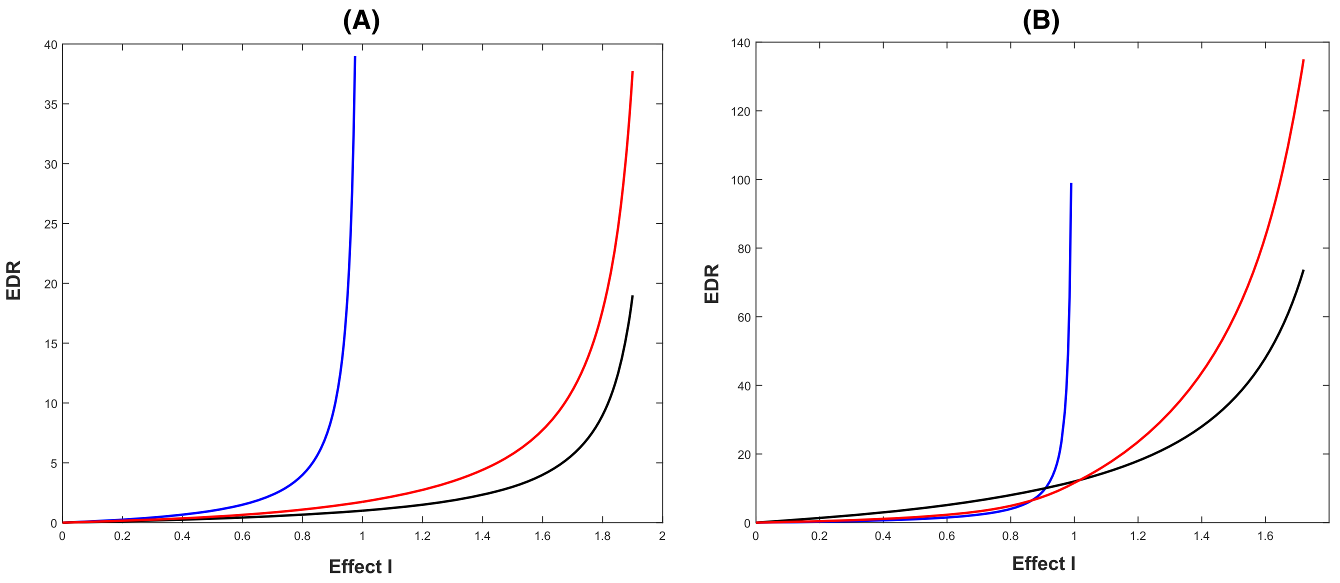

FIGURE 10 (A) Combination EDR for two DERs with distinct finite ranges of effect that has the betweenness property. 1-agent EDRs are $F_1(I) = I/(1\text{-}I)$ (blue curve) and $F_2(I) = I/(2\text{-}I)$ (black curve). The combination EDR (red curve) is given by Equation (5.3.2) with $a = b = 1$. (B) Combination EDR for two DERs with distinct finite ranges of effect that violates the betweenness property. 1-agent EDRs are $F_1(I) = I/(1\text{-}I)$ (blue curve) and $F_2(I) = I/(2\text{-}I)$ (black curve). The combination EDR (red curve) is given by Equation (5.3.2) with $a = 1$, $b = 12$. [Colour figure can be viewed at wileyonlinelibrary.com]

In fact, it follows from Equation (5.3.2) that the combination EDR and the EDR for agent 2 intersect for $I^* = 2(12\text{-}C)/(18\text{-}C)$, where

$$C = \sqrt{2ab}\left[\tan^{-1}\frac{\sqrt{2}(a+b)}{\sqrt{ab}} - \tan^{-1}\sqrt{\frac{a}{2b}}\right],$$

which for $a = 1$, $b = 12$ yields $I^* \cong 1.017 > 1$. In the case $h_2 = \infty$, the same effect is illustrated by the following example that modifies Example 6.

Example 9. Let $N = 2$, $r_1 = r_2 = 0.5$, $h_1 = 11/9 \cong 1.222$, and $h_2 = \infty$. Suppose $F_2(I)$ is given by Equation (5.2.4) and

$$F_1(I) = \begin{cases} I & \text{for } 0 \le I < 1.1 \\ \dfrac{1.21}{11 - 9I} & \text{for } 1.1 \le I < \dfrac{11}{9} \end{cases} \tag{5.3.3}$$

Using Equation (3.3.3), we obtain

$$F(I) = \begin{cases} I/3 & \text{for } 0 \le I < 1 \\ 5I/3 - 4/3 & \text{for } 1 \le I < 1.1 \\ \dfrac{1}{2} + \dfrac{11}{15}\left[\tan^{-1}\dfrac{1}{3} - \tan^{-1}\left(\dfrac{10}{3} - \dfrac{30}{11}I\right)\right] & \text{for } 1.1 \le I < \dfrac{11}{9} \\ 2I + \dfrac{11}{15}\tan^{-1}\dfrac{1}{3} - \dfrac{35}{18} & \text{for } I \ge \dfrac{11}{9} \end{cases} \tag{5.3.4}$$

For $I = h_1 = 11/9$, where agent 2 is dropped off from Equation (3.3.2), we have

$$F\left(\frac{11}{9}\right) = \frac{1}{2} + \frac{11}{15}\tan^{-1}\frac{1}{3} \cong 0.736$$

while

$$F_2\left(\frac{11}{9}\right) = \frac{11}{9} - 0.4 \cong 0.822.$$

Also, it follows from Equations (5.2.4) and (5.3.4) that the unique solution of the equation $F(I) = F_2(I)$ on the interval $[11/9, \infty)$ is

$$I^* = \frac{139}{90} - \frac{11}{15}\tan^{-1}\frac{1}{3} \cong 1.308.$$

Therefore, on the interval $[h_1, I^*)$, the combination EDR curve stays below the remaining EDR curve for agent 1; see Figure 11.

5.4 | Efficiency of our computational methodology

To demonstrate the efficiency of our computational methodology, we compute HIEA EDR for a combination of four agents, one having a finite range of effects and DER that is "extremely flat" at the origin and others having infinite range of effects including one agent with infinite derivative at the origin. Specifically, suppose $E_1(d) = \exp(-1/d)$ for $d > 0$ and $E_1(0) = 0$, $E_2(d) = \ln(d + 1)$, $E_3(d) = d + d^2/2$, and $E_4(d) = d^{1/2}$. Then for the respective 1-agent EDRs, we obtain $F_1(I) = 1/\ln(1/I)$, $F_2(I) = \exp(I)$-1, $F_3(I) = (2I + 1)^{1/2}$-1, and $F_4(I) = I^2$. Assuming that the doses contributed by the four agents are equal, we find from Equation (3.3.3) that

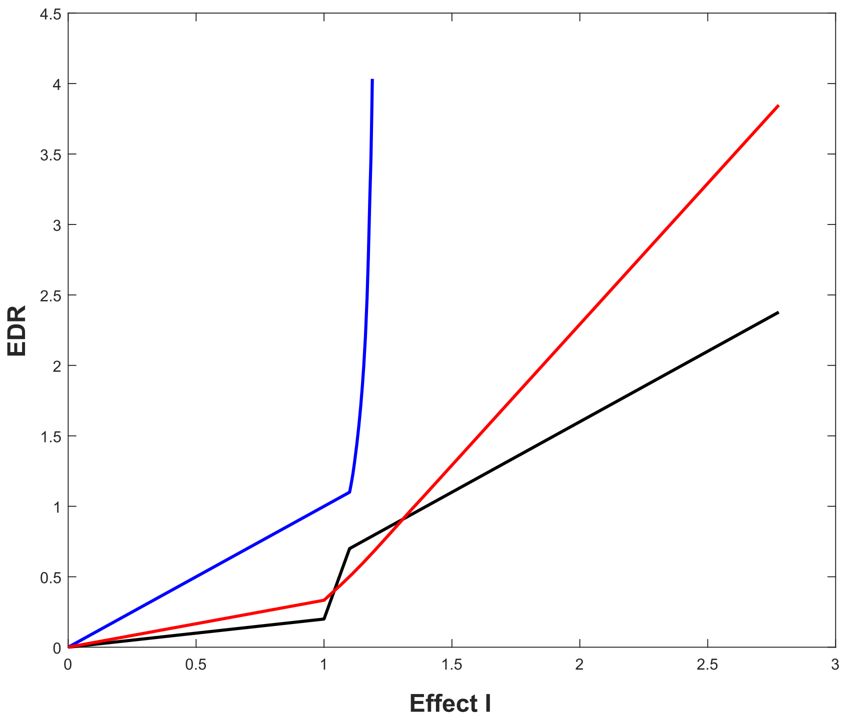

FIGURE 11 Combination of two agents having DERs with distinct (one finite and one infinite) ranges of effect may violate the betweenness property but always has the eventual betweenness property. $F_1(I)$ (blue curve) is given by Equation (5.3.3), and $F_2(I)$ (black curve) is given by Equation (5.2.4). The 1:1 combination NSNA EDR is given by Equation (5.3.4) (red curve). In the effect interval (11/9, I^*) ~ (1.222, 1.308), the red curve lies below the remaining 1-agent DER, but on the effect interval (I^*, ∞) betweenness holds in the sense that the red curve stays above the black curve. [Colour figure can be viewed at wileyonlinelibrary.com]

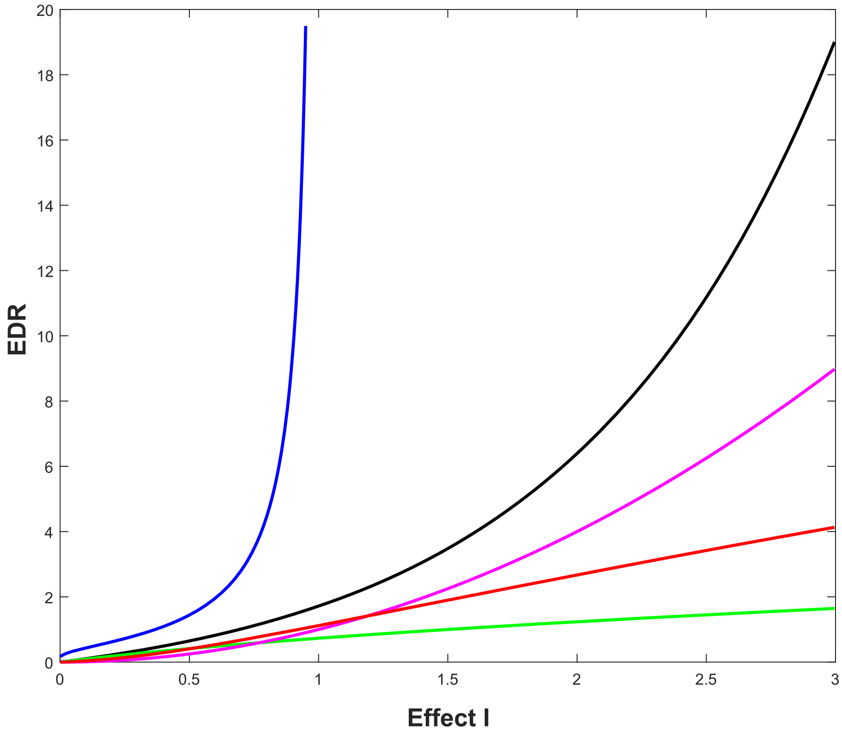

FIGURE 12 Combination HIEA NSNA EDR for four agents with different (one finite and three infinite) ranges of effect. EDRs of the four agents are $F_1(I) = 1/\ln(1/I)$ (blue curve), $F_2(I) = \exp(I)$-1 (black curve), $F_3(I) = I^2$ (magenta curve) and $F_4(I) = (2I+1)^{1/2}$-1 (green curve). Note that although betweenness holds, the combination HIEA EDR (red curve) is surprisingly low, a signal that even though other criteria may be suggesting synergy, the NSNA HIEA EDR may be pointing to antagonism instead. The combination EDR is given by Equations (5.4a) and (5.4b). [Colour figure can be viewed at wileyonlinelibrary.com]

$$F(I) = 8\int_0^I \frac{xdx}{2(x\ln x)^2 + 2xe^{-x} + 2x\sqrt{2x+1}+1}, \quad 0 \le I \le 1. \tag{5.4a}$$

Clearly, the integrand doesn't have a singularity at 0 or 1. Furthermore, for $I > 1$,

$$F(I) = F(1) + 8\int_1^I \frac{xdx}{2xe^{-x} + 2x\sqrt{2x+1}+1}. \tag{5.4b}$$

The 1-agent EDRs and the combination EDR obtained by numerical integration are shown in Figure 12.

6 | DISCUSSION AND CONCLUSIONS

In this article, we studied major synergy theories that are widely used in radiation biology, pharmacology, toxicology, and other biomedical sciences. The principal focus of this work was on rigorous formulation and mathematical analysis of the most recent among these theories, HIEA.

6.1 | SEA and its replacements

SEA synergy theory needs to be replaced—synergy theories that fail to obey the sham combination principle and a more general combination of combinations principle are not self-consistent and should be avoided. But our results showed that no fully satisfactory replacement is currently known. The two most promising candidates, LBA and HIEA, have the following pros and cons of their own:

(1) LBA often fails to provide a good approximation to empirical data on joint effects of non-interacting agents. On the positive side, we showed the theory has the important betweenness property.
(2) HIEA often flunks the betweenness test, as our Sections 5.2 and 5.3 document in detail. Furthermore, for some collections of 1-agent regular DERs (i.e., those with finite effect for any finite dose), their combination, even in the absence of synergy or antagonism as defined by the HIEA equation, may prove singular, that is, produce infinite effect for finite dose, which represents an extreme case of betweenness violation. Such forbidden collections of agents are fully characterized in terms of their EDRs or ESFs in Section 4.2. In particular, it is shown that the presence of a strongly dominant agent prevents the singularity phenomenon.
(3) Both synergy theories can handle readily 1-agent DERs with distinct ranges of effect; see Section 5.3. The methodology consists of dropping from the NSNA equation the terms for the agents whose maximum effect is smaller than the given value of the combination effect. Since this methodology is dictated by mathematical convenience (preservation of NSNA equation continuity), only empirical studies can ultimately determine whether the agents dropped from the equation have no impact at all on the combination effect levels they cannot reach on their own.
(4) Both LBA and HIEA synergy theories cannot deal with combinations of agents whose DERs are not monotonic increasing.

6.2 | HIEA betweenness violation

Violation of the betweenness property by HIEA is a troubling phenomenon. In the case of two agents, it amounts to the existence of a certain region in the (effect, dose) plane where the combination EDR curve lies below EDR curves of these agents; see Figures 4, 6, 7B, 8, 9B, 10B, and 11. By definition of NSNA criterion, this region lies in the antagonism domain; see Figure 1. In spite of this, dose coordinates of points on the combination EDR curve within this region are combination doses that are more effective than equal doses of both agents, which would intuitively suggest synergy.

In modeling accelerator experiments with ion mixtures designed to simulate the interplanetary GCR environment, HIEA happened to obey betweenness in each considered instance [7]. The possibility of betweenness violation, discovered and studied in considerable detail in this article, has come as a surprise. Some of the results of this work provide welcome sufficient conditions for betweenness to hold; one of them is Proposition 5.2.3 on dominant agents. Nevertheless, betweenness will henceforth be an issue in applications of HIEA.

It has been suggested in Sinzger et al. [5] that HIEA is a more biochemically plausible synergy theory than LBA. However, in view of the betweenness violation by HIEA, this may not be the final word. We suggest comparing the two synergy theories for many data sets, including some radiobiology data sets with many components, before deciding which of the two synergy theories, if either, is more useful.

6.3 | Future prospects

High throughput testing of combinations of various substances has produced a copious amount of data; see, for example, studies [3, 5, 6, 31] and references therein. Biologists and modelers studying such data will surely continue to look for models and theories allowing to detect possible synergy or antagonism and use them to plan experiments and interpret their results. Among the reasons for the importance of synergy theories are the extra dangers brought about by drastic deleterious synergy and, in the case of beneficial synergy, achieving greater therapeutic effect with smaller doses and reduced toxicity.

It should not be taken for granted that the result of a combination experiment confirming expectations from 1-agent experiments must necessarily be less valuable than a result contradicting such expectations. For example, stochastic track structure considerations, fundamental in radiobiology, arguably suggest that mixtures of many different densely ionizing radiations may have stochastic ionization patterns not so different from those of a single densely ionizing beam, so that at low doses marked deviations from 1-beam action patterns may not occur. If, for mixtures of densely ionizing radiations in experiments on damaging endpoints, evidence against deviations from NSNA action accumulates, that will be more important, and more welcome, than would a novel and exciting finding of major synergy for some specific mixture.

Given that synergy theory will continue to be emphasized, trying to find a systematic, quantitative, precisely defined approach to agent interaction that is general enough to cover most cases of interest and is self-consistent seems a worthwhile endeavor.

AUTHOR CONTRIBUTIONS

Leonid Hanin: Conceptualization; formal analysis; investigation; methodology; software; visualization; writing—original draft; writing—review and editing. **Liyang Xie:** Data curation; investigation; software; visualization. **Rainer Sachs:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; visualization; writing—original draft; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no competing interests.

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