Appendix A5. Generalizing Incremental Effect Additivity Synergy Theory

A5.1. The Equation for *I*(*d*)

Prior to the availability of computers which can rapidly provide accurate numerical solutions to

non-linear ODE, it was natural to specify 1-agent DERs by giving effect as an appropriate

explicit function $E=E(d)$ of dose, as in [Cacao et al. 2016], in [Cucinotta and Cacao 2017], and

in very many other papers. We suggest that nowadays it is often preferable to specify 1-agent

DERs via their slope as a function of E itself, by solving an ODE IVP (initial value problem) of

the form

$$\text{(A5.1)} \quad \text{(A)} \quad dE / dd = F(E); \quad \text{(B)} \quad E = 0 \text{ when } d = 0,$$

with the slope function $F(E)$ sufficiently well behaved that there is one and only one solution for

all sufficiently small non-negative doses. Additional requirements on $F(E)$, e.g. the requirement

that the solution not approach ± infinity as dose approaches some finite value from below, will

be analyzed in subsequent sub-sections. Eq. (A5.1A) is what is called an "autonomous" ODE,

referring to the fact that $F(E)$ depends only on E, with no explicit dose dependence, and Eq.

(A5.1) is called an autonomous IVP (AIVP).

 Some motivations for taking F as a function of E rather than a function of d are similar to

some of the motivations for using incremental effect additivity $I(d)$. E, unlike d, is a state

variable, determined by the changing state of the target system as dose and effect accumulate

[Lam 1994]. Moreover, mechanistically analyzing how a small increment of effect interacts with

effects caused by earlier dose increments is sometimes easier than mechanistically analyzing the

entire effect of the entire dose [Lam 1987].

Consider a mixture consisting of $N \geq 0$ agents whose 1-agent DERs are AIVPs. Let r_1, r_2, ...,
r_N be the corresponding proportions. The general equation of incremental effect additivity for
$I(d)$ with d being total mixture dose is:

(A5.2) $\quad dI / dd = \sum_{j=1}^{N} r_j F_j(I); \quad d = 0 \Leftrightarrow I = 0.$

Importantly, a monotonic $I(d)$ baseline MIXDER can often be calculated with Eq. (5.2) for

mixtures some of whose 1-agent DERs have $F(E) < 0$ while others have $F(E) > 0$. This

surprising relaxation of the exasperating restriction that all 1-agent DERs be monotonic in the

same direction is discussed in more detail in sub-section A5.3 below. It is a far-reaching

generalization if we can: (a) find simple necessary and sufficient conditions to exclude

unsuitable behavior such as $I(d)$ shooting up or down to ± infinity at finite doses, as exemplified

in Fig. A5.2 below; and (b), find a sufficiently general set of 1-agent DERs to approximate the

many different situations encountered in experiments in various STEM fields.

Generalized incremental effect additivity synergy theory consists of analyzing the solution of

Eq. (A5.2) when each component has an appropriate 1-ion DER..

A5.2. 1-agent DERs Defined by Solving Autonomous IVPs (AIVPs)

Using 1-agent DERs that are defined by Eq. (A5.1) instead of being given as functions of dose is

essential for using the general equation, Eq. (A5.2), to calculate $I(d)$. However this approach is

unfamiliar. This sub-section, A5.2, describes some differences in the two approaches, shows that

there are many functions $F(E)$ in Eq. (5.1) which allow explicit calculation of the corresponding

$E(d)$, shows that not all functions $F(E)$ lead to suitable $E(d)$, and suggests an approach, using

functions of a complex variable, to trying to find simple necessary and sufficient conditions on

$F(E)$ for $E(d)$ to be suitable.

A5.2.1. Slope Addition vs. Function Addition

Some of the 1-agent DERs we used in the main text involved adding two terms, for NTE and TE respectively. The corresponding approach when using AIVPs, to add two slopes, gives somewhat different results. Specifically, suppose the slope $F(E)$ in Eq. (A5.1) is modeled as a sum of two terms:

$$(A5.3) \quad dE/dd = F_1(E) + F_2(E).$$

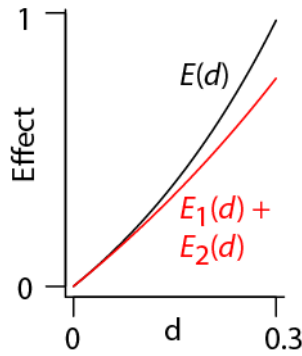Then $E(d)$ is in general not merely the sum of the two AIVPs defined by

$$(A5.4) \quad dE_1/dd = F_1(E), \ E_1(0) = 0; \quad dE_2/dd = F_2(E), \ F_2(0) = 0.$$

For example consider the following, with $F_1(E)$ and $F_2(E)$ both chosen to be linear so that solving all three AIVPs given by Eqs. (A5.3) and (A5.4) is simple

$$(A5.5) \quad F_1(E) = 1 + E, \text{ and } F_2(E) = 1 + 2E \Rightarrow F(E) = 2 + 3E.$$

Integrating each of the three AIVPs explicitly gives

$$(A5.6) \quad E_1 = \exp(d) - 1; \quad E_2 = (1/2)[\exp(2d) - 1]; \quad E = (2/3)\left[\exp(3d) - 1\right].$$

So $E(d) > E_1(d) + E_2(d)$, as shown in the Figure. In fact, this inequality holds whenever both $F_1(E)$ and $F_2(E)$ are positive monotonic increasing functions for all relevant E, with all three 1-agent DERs involved then necessarily being convex.

The result $E(d) > E_1(d) + E_2(d)$ contrasts with the result where a slope is determined by functions of dose. For any integrable functions $F_1(d)$ and $F_2(d)$ we have

$$dE/dd = F_1(d) + F_2(d) \Rightarrow E = \int F_1 + \int F_2 + cons. \Rightarrow E(d) = E_1(d) + E_2(d).$$

Here the second implication follows from the fact that all 3 effects are 0 at dose zero.

A5.2.2. Examples of Explicit 1-agent DERs Defined by Eq. (A5.1).

Over the years, radiobiologists have developed 1-agent DER equations given by explicit equations to fit various biophysically motivated and/or experimentally observed curve shapes. Examples include multi-target, multi-hit equations, amorphous track structure equations, LQ equations, many generalizations of LQ equations, equations incorporating NTE, etc. In Eq. (A5.1) one instead starts with the slope $F(E)$. Often no explicit equation for $E(d)$ itself can be found. Finding $E(d)$ then involves using a standard ODE integrator such as the function ode() in the package deSolve of the computer language R and results in a numerical version of $E(d)$. Subsequent calculations then either just use this numerical form to get further numerical results or use the qualitative theory of ODE [Brauer and Nohel 1989], which involves analyzing slopes to determine solution properties without attempting to actually integrate an ODE.

However we will now show by examples that there are many cases where the IVP (A5.1) can be solved explicitly. Such explicit 1-agent DERs, and methods for generating them from Eq. (A5.1), are often useful, in helping understand numerical 1-agent DERs, when debugging customized software, and to supplement results obtained from the qualitative theory of ODE.

Suppose we have $N+1$ real numbers: $c > 0$; and $a_k \neq 0$, with $k=1, 2, …, N$. Suppose no two a_k are equal. In Eq. (A5.1) suppose

$$(A5.7) \quad F(E) = c \prod_{k=1}^{N} (a_k + E).$$

Thus $F(E)$ is an Nth degree polynomial with non-zero, distinct real roots $-a_k$. In this case one can always use the method of partial fractions to integrate the ODE (A5.1) and obtain d as a smooth monotonically increasing or monotonically decreasing function of E on some half-open interval $[0,A)$. Sometimes the inverse function $E(d)$ can be expressed explicitly. For example when $N=1$ and $a>0$ the solution $E(d)$ obtained by integrating and using an inverse function involves an exponential:

$$F(E) = c(a+E) \Leftrightarrow d = \frac{ln(a+E) - ln(a)}{c}$$

$$(A5.8)$$

$$\Leftrightarrow E(d) = a\exp(cd) - a \Rightarrow E'(0) = ca, \ E''(0) = c^2 a.$$

$E(d)$ is then similar to an LQ curve with both α and β positive in the following respects: for doses so small terms cubic or higher in dose can be neglected, $E(d)$ is LQ with $\alpha=ca$ and $\beta=(c/2)\alpha$; $E(d)$ is strictly convex, with positive second derivative, for all doses (Fig. A5.1 below); $E(d)$ does not approach ∞ as some finite value is approached by d; and $E(d)$ is unbounded, approaching ∞ as d approaches ∞.

As another example, for $N=2$ with $a, b, c>0$ one has:

$$(A5.9) \quad F(E) = c(a+E)(b-E) \Leftrightarrow E = \frac{a\exp[(a+b)cd] - a}{1 + (a/b)\exp[(a+b)cd]}.$$

In this case $E(d)$ approaches b as d approaches ∞ and, depending on the choice of parameters, the curve can be concave or sigmoidal (Fig. A5.1).
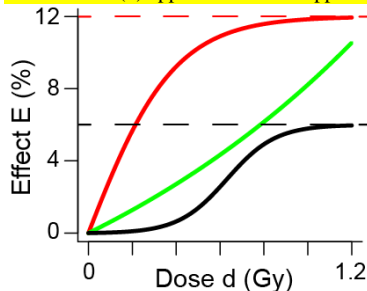

Fig. A5.1. Curve shapes. All three curves are monotonically increasing with finite positive slope at all doses. The green curve is described explicitly by Eq. (A5.8) with $a=10$ and $c=0.6$. It has properties similar to an LQ curve; at low doses it is LQ, with $\alpha= 6\%$ per Gy and $\alpha/\beta=10/3$ Gy. The black curve and red curves are described by Eq. (A5.9) with upper limits $b=6\%$ or 12% respectively. The black curve has $a=0.02$ and has $c=1.5$; it is sigmoidal, with a point of inflection.

The red curve has $a=13$ and has $c=0.2$. It is concave. The criterion for concavity vs. sigmoidicity is $a>b$ vs. $a<b$. It is seen that one can readily find AC 1-agent DERs with explicit $E(d)$ functions and various qualitatively specified shapes.

A5.2.3. Unsuitable Slope Functions F(E)

Some solutions of Eq. (5.1) approach infinity as dose approaches some finite value from below.

For example, with ξ a real constant > 0 suppose $F(E)$ in Eq. (A5.1) is $F=\xi(1+E^2)$ Gy^{-1}.

Integrating $dE/(1+E^2)$ gives E=tangent(ξd). In the interval $[0, \pi/2\xi)$ the 1-agent DER is smooth.

However, as d approaches $\pi/2\xi$ from below, E approaches infinity, as shown in Fig. A5.2.
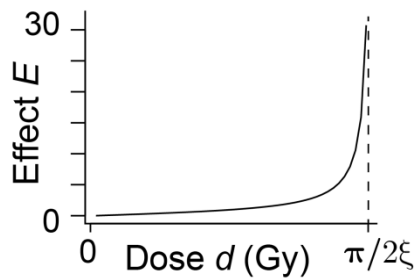

Fig. A5.2. The 1-agent DER E=tan(ξd).

A 1-agent DER that approaches ∞ at finite dose is not useful in any radiobiology analysis we know of, and attempts to use synergy theories on a mixture one of whose components has 1-agent DER $E(d)$=tan(ξd) give strange components has 1-agent DER $E(d)$=tan(ξd) give strange

results, with that component completely dominating mixture behavior. We therefore consider the

1-agent DER tan(ξd) unsuitable.

A5.2.4. Analytically Defined 1-agent DERs (AC 1-agent DERs).

In practice unsuitable 1-agent DERs that are explicit functions of dose, such as those in

subsection A5, are easily avoided. However until/unless one finds simple necessary and

sufficient conditions on $F(E)$ for the implied 1-agent DER, which is an AIVP and not an explicit

function of dose, to be suitable, incremental effect additivity must remain somewhat

unsatisfactory as a mathematical theory. This sub-section discusses some aspects of that problem

and suggests a possible solution.

To decide on candidate slope functions $F(E)$ for suitable 1-agent DERs we reasoned that the

motivation involved an extrapolation and, mathematically speaking, complex analysis

encourages extrapolations. In Eq. (A5.1) $F(E)$ is a real function of a real variable, but instead of

choosing $F(E)$ directly we can, and in this sub-section will, assume $F(E)$ is specified using a complex function G of a complex variable, with G chosen to approximate whatever is known or inferred about the 1-agent DER slope. We will call G a "slope extrapolator".

Specifically, we assume that $F(E)$ is the restriction of $G(z)$, with z the complex variable $z=E+iy$, to the non-negative E axis (horizontal axis) in the complex plane, where G is holomorphic in some open neighborhood of the origin z=0 (i.e. $E=0=y$). For example any polynomial $F(E)$ is such a restriction of $G=F(E+iy)$, so all the examples in Fig. A5.1 above can be defined by such a G. In general we call an 1-agent DER defined by Eq. (A5.1) and a function $G(z)$ holomorphic in some neighborhood of $z=0$ an "Analytically-Characterized" 1-agent DER (AC 1-agent DER).

Suppose throughout the rest of this sub-section that the slope extrapolator $G(z)$ is a polynomial of (finite) degree M greater than 0 with real coefficients a_j. Thus $G(z)$ has no singularities in the complex plane (i.e. on the finite part of the extended complex plane). Suppose first the only zeros of $G(z)$ lie on the imaginary axis. Then it follows that M is even, that $a_M>0$, and, since $a_M E^M$ increases at least as fast as E^2 for large E, that $E(d)$ is unsuitable because it approaches infinity for some finite d. On the other hand suppose all zeros of $G(z)$ lie on the real line with at least one zero for $E>0$. Then the qualitative theory of ODE [Brauer and Nohel 1989] shows that $E(d)$ approaches that zero on the positive real axis which is closest to the origin; Fig A5.1 shows specific examples; it happens that $E(d)$ can be found explicitly in these specific examples, but that is not a major consideration in the present argument. The AC 1-agent DERs shown in Fig. A5.1 are suitable.

To summarize, by placing restrictions on the location in the complex plane of the slope extrapolator's zeros in a case where there are no singularities and a finite number of zeros, we

have been able to generalize, obtaining criteria for suitable and unsuitable AC 1-agent DERs in that case. The calculations were rendered mathematically very simple by starting with the assumption that G is a polynomial, ~~an assumption far too strong to be used as a general restriction~~; Yimin's key insight is that this polynomial assumption can always be made because we are never interested in very large doses in practice. This insight makes it possible to explore systematically whether AC 1-ion AIVP DERs can, by adjusting the order of the polynomial and its zeros in the complex E+iy plane, be made sufficiently general to handle the various dose-effect relations that inspection of real data and conceptual arguments lead to in experimental STEM fields. If so, this approach is, as shown by many examples (omitted here) we have considered, a major breakthrough, far more useful than any previously published synergy theory dealing with scalar effects.