DRAFT: A Categorical Formulation of Dose-Escalation Designs

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September 17, 2024

1 Introduction

Notation 1.1. *The* ***dose levels*** *— or more simply,* ***doses*** *— of a dose-escalation trial are a strictly ascending finite sequence* $(x_1 < ... < x_D)$ *of dose intensities* $x_d \in \mathbb{R}^+$*. The formulation advanced here refers to these doses by their indices* $\{1, ..., D\}$*, preserving their order but abstracting away from their numerical magnitudes.*[1]

Notation 1.2. *The* ***participants*** *in a dose-escalation trial, indexed by* $i \in I$*,* ***enroll*** *at time* t_0^i *into dose* d^i*. Given that toxic responses generally manifest with some latency after dose administration,* ***toxicity assessment*** *remains* ***pending*** *for participant* i *until some time* $t_1^i \in (t_0^i, t_0^i + \delta t]$ *when the assessment* ***resolves*** *into one of three* ***outcomes****:*

- *Participant* i *is found to have experienced an (intolerable)* ***toxicity****,*
- *to have become* ***inevaluable*** *due e.g. to early withdrawal from the trial or death unrelated to toxicity,*
- *or otherwise (at* $t_1^i = t_0^i + \delta t$*) is assessed to have* ***tolerated*** *their dose.*[2]

Notation 1.3. *We denote evaluability by* $n^i \in \{0, 1\}$ *and the outcome of toxicity assessment by* $y^i \in \{0, 1\}$*.*

Notation 1.4. *We write* $I_d(t) \subseteq I$ *for the subset of individuals enrolled at dose* d *whose assessments have resolved by time* t*:*

$$I_d(t) = \{i \in I \mid d^i = d, \, t_1^i \leq t\}.$$

[1] But in what follows, it will be seen that a few general premises about the quantitative spacing of the dose levels will be important for justifying certain heuristics.

[2] Our formulation ignores late-manifesting toxicities that occur after the lapse of time δt.

Definition 1.5. *A* ***dosewise tally*** *is an ordered pair* $(t, n) \in \mathbb{N} \times \mathbb{N}$*, recording the assessment of* $t \leq n$ *toxic responses among* n *evaluable trial participants who have received that dose. These will be freely denoted with fraction bars as* t/n *or* $\frac{t}{n}$*, or in ratio form as* $t\!:\!u \equiv t/(t+u)$*. Note that* $0/0$ *represents a valid dosewise tally.*

Notation 1.6. *We will denote the set of dosewise tallies by* $Q = \{t/n \mid t, n \in \mathbb{N}; t \leq n\}$ *or* $R = \{t\!:\!u \mid t, u \in \mathbb{N}\}$ *as needed. We will also write elements of* Q^D *or* R^D *using the same notation, with context dictating that* $t, n, u \in \mathbb{N}^D$*.*

Observe that Q equipped with a $+$ operator defined naturally,

$$\frac{t_1}{n_1} + \frac{t_2}{n_2} = \frac{t_1 + t_2}{n_1 + n_2},$$

is a commutative monoid, with identity $0/0$. This property extends in the obvious way to Q^D.

Definition 1.7. *A* ***[full] tally*** *is a vector* $q = (q_1, ..., q_D) \in Q^D$ *giving the dosewise tally for each dose in an ascending sequence indexed by* $\{1, ..., D\} \subset \mathbb{N}$*.*

Definition 1.8. *The* ***cumulative tally*** *is a right-continuous function of time,*

$$q : \mathbb{R}^+ \to Q^D,$$

with dosewise components

$$q_d(t) = \sum_{i \in I_d(t)} \frac{y^i}{n^i}.$$

Definition 1.9. *The* ***pending count*** *is a right-continuous function of time,*

$$p : \mathbb{R}^+ \to \mathbb{N}^D,$$

with dosewise components

$$p_d(t) = |\{i \in I \mid d^i = d,\, t_0^i \leq t < t_1^i\}|.$$

Definition 1.10. *The* ***state*** *of a dose-escalation trial is an ordered pair consisting of the cumulative tally and pending count:*

$$s(t) = (q(t), p(t)).$$

This state sums up what is known at time t *about all the participants who have enrolled by then: those who proved inevaluable contribute* $0/0$ *to* q*; those who did or did not tolerate the drug contribute* $0/1$ *or* $1/1$*, respectively; and those whose assessments remain pending are counted in* p*.*

Notation 1.11. *By implicitly regarding* t *as an arbitrary 'current time' or 'now', we will often freely suppress the* t*-dependence of* I_d*,* q*,* p *and* s*.*

Notation 1.12. *Denote by* $S = Q^D \times \mathbb{N}^D$ *the range of* $s : \mathbb{R}^+ \to S$.

Notation 1.13. *For* $s \in S$, *let* $\underline{s}$ *denote the first component and* $\bar{s}$ *the second:*

$$s \equiv (\underline{s}, \bar{s}).$$

Definition 1.14. *For* $p \in \mathbb{N}^D$, *we regard the* ***pending assessment*** *as the set,*

$$\surd p = \{\frac{t}{n} \in Q^D \mid n \leq p\} \subset Q^D,$$

of all its possible resolutions. The surd notation $\surd$ *is meant to convey the idea that* $\surd p$ *represents the unresolved potentiality of pending assessments that have 'not yet spoken' [L.* surdus, *mute]. The angular appearance of* $\surd$ *also serves to remind of the triangular shape of each dosewise component* $(\surd p)_d \subset Q \subset \mathbb{N}^2$. *Pronouncing* $\surd$ *'res' instead of 'root' in this context may help.*

Notation 1.15. *Let* $A = \surd\mathbb{N}^D = \{\surd p \mid p \in \mathbb{N}^D\} \subset 2^{Q^D}$ *denote* $\surd$*'s range.*

Fact 1.16. *For any pending assessment* $\surd p$, *it is possible to recover the vector* p *from the maximal denominator:*

$$\bigvee \{n \mid t/n \in \surd p\} = p.$$

To see this, simply consider any resolution in $\surd p$ *with all participants evaluable.*

Fact 1.17. *The mapping* $\mathbb{N}^D \xrightarrow{\surd} A$ *thus establishes an isomorphism:*

$$\mathbb{N}^D \cong A \subset 2^{Q^D}.$$

Fact 1.18. *Accordingly, we may regard* S *as the direct sum,*

$$S = Q^D \times \mathbb{N}^D \cong Q^D \oplus A,$$

writing its individual elements (i.e., states) as,

$$s = \underline{s} \oplus \surd\bar{s},$$

thereby conceptualizing states as ***sets of possible tallies****:*

$$s = \{\underline{s} + a \mid a \in \surd\bar{s}\} \subset Q^D.$$

Notation 1.19. *We formalize this understanding by extending* $\surd$ *to a function on* S, *and writing* $Q^D \times \mathbb{N}^D = S \cong \surd S = Q^D \oplus A \subset 2^{Q^D}$.

Definition 1.20. *The* ***plurality*** *of a state* $s \in S$, *denoted* $|s|$, *is defined as*

$$|s| = |\surd s| = |\surd\bar{s}|.$$

Definition 1.21. *A state* $s \in S$ *is* ***singular*** *if* $|s| = 1$ *and* ***plural*** *if* $|s| > 1$.

Notation 1.22. *For any set X, the power set 2^X is customarily identified with the preorder (hence, category) $(2^X, \subseteq)$. The opposite category $(2^X)^{\text{op}}$ is then the preorder $(2^X, \supseteq)$.*

Notation 1.23. *Let $\mathcal{S} = (S, \supseteq)$ denote the preorder obtained as the (full) subcategory of $(2^{Q^D})^{\text{op}}$ defined by $\surd$ as an inclusion functor $\mathcal{S} \xhookrightarrow{\surd} (2^{Q^D})^{\text{op}}$.*

By choosing to embed $\mathcal{S}$ in the *opposite* (dual) category of 2^{Q^D} we obtain arrows $\supseteq$ that point *in the direction of time*, as pending evaluations resolve and *information increases*.

Notation 1.24. *Let $\mathcal{A} = (A, \supseteq)$ denote the preorder obtained from the embedding of $A \subset 2^{Q^D}$. Observe that $\mathcal{A}$ may be regarded as a subcategory of $\mathcal{S}$ via the inclusion functor $0 \oplus -$:*

$$\mathcal{A} \xhookrightarrow{0\oplus-} \mathcal{S} \tag{1}$$

$$\sqrt{p} \mapsto (\frac{0}{0}, ..., \frac{0}{0}) \oplus \sqrt{p}. \tag{2}$$

Notation 1.25. *We extend $\oplus$ to a bifunctor $\mathcal{S} \times \mathcal{A} \xrightarrow{\oplus} \mathcal{S}$:*

$$s \oplus \sqrt{p} = \underline{s} \oplus \sqrt{(\bar{s} + p)},$$

modeling the possibility of enrolling additional participants into a still-plural state s with nonzero pending count $\bar{s}$.

Fact 1.26. *Augmenting $\mathcal{S}$ to include the initial object $U = Q^D$ and the terminal object $\emptyset$, we obtain obtain a symmetric monoidal preorder, $\mathcal{S}^* = (S^*, \supseteq, U, \cap)$ with set intersection as the monoidal product and U as its unit. The essence of the proof is showing that $S^* = \sqrt{S} \cup \{\emptyset, U\}$ is closed under set intersections. This is readily appreciated from the geometry of the components $(\sqrt{s} \cap \sqrt{s'})_d$ as intersecting isosceles right-triangular subsets of $Q \subset \mathbb{N}^2$. (The formal proof may be slightly easier in the plane of $R \cong \mathbb{N}^2$, where the elements $t\!:\!u$ admit a symmetrical treatment of their t and u parts.)*

Fact 1.27. *The above holds true for any choice of $U \subset Q^D$, provided that we take the elements of $\mathcal{S}^*$ to be $\{s \cap U \mid s \in \sqrt{S}\}$. This allows for U to define a bounded set of* ***accessible tallies****, such as might arise from a fixed limit on trial enrollment.*

Note that the 'null state' $\emptyset$ is a pure abstraction, unlike the *actual* state $\frac{0}{0} \oplus 0$ which we might well regard as obtaining upon initiation of the trial. The 'universe' U is likewise an abstraction which would never obtain as an actual trial state, except in the (pathological) case where the entire planned enrollment were achieved before any assessments completed.

2 Modeling Pharmacologic Monotonicities

Definition 2.1. *Let $+ : Q \times Q \to Q$ be defined by*

$$\frac{t_1}{n_1} + \frac{t_2}{n_2} = \frac{t_1 + t_2}{n_1 + n_2}.$$

Observe that this is a monoidal operation with unit $0/0$, which extends in the obvious way to a monoidal operation on Q^D with unit $(\frac{0}{0}, ..., \frac{0}{0})$.

Definition 2.2. *Let $\preceq$ be the transitive closure of a preorder relation satisfying,*

$$\frac{t}{n} + \frac{1}{1} \preceq \frac{t}{n} \preceq \frac{t}{n} + \frac{0}{1} \quad \forall \frac{t}{n} \in Q. \tag{3}$$

Then the preorder $(Q, \preceq)$ compares the ***evident safety*** *expressed in dosewise tallies, such that we read*

$$q_1 \preceq q_2$$

as "q_1 is evidently no safer than q_2" or "q_2 is evidently at least as safe as q_1".

Fact 2.3. *$(Q, \preceq, \frac{0}{0}, +)$ is a symmetric monoidal preorder. It is easy to see that $+$ is a symmetric monoidal operation on Q with unit $0/0$, the necessary unitality, associativity and commutativity all being inherited directly from the monoid $(\mathbb{N}, 0, +)$. The monotonicity condition.*

$$q \preceq q',\ g \preceq g' \implies q + g \preceq q' + g',$$

arises by induction from the Definition 2.2 of $\preceq$ in terms of $+$.

Fact 2.4.

$$\frac{t}{n} \preceq \frac{t'}{n'} \qquad \Longleftrightarrow \qquad t \geq t' + \max(0, n - n').$$

Proof. This is most easily seen by expressing (3) in its equivalent ratio form,

$$t\!:\!u + 1\!:\!0 \preceq t\!:\!u \preceq t\!:\!u + 0\!:\!1 \quad \forall\, t\!:\!u \in R,$$

and observing that consequently $t : u \preceq t' : u'$ iff $t \geq t'$ and $u \leq u'$. This latter condition, in turn, may be transformed as follows:

$$\begin{aligned} & t \geq t' \ \wedge\ u \leq u' \\ \Longleftrightarrow\quad & t \geq t' \ \wedge\ n - t \leq n' - t' \\ \Longleftrightarrow\quad & t \geq t' \ \wedge\ t \geq t' + (n - n') \\ \Longleftrightarrow\quad & t \geq t' + \max(0, n - n'). \end{aligned}$$

$\square$

Notation 2.5. *Let $\langle q \rangle_j$ denote the tally $(\frac{0}{0}, ..., \frac{0}{0}, q, \frac{0}{0}, ..., \frac{0}{0}) \in Q^D$ with $q \in Q$ in the j'th position and $0/0$ elsewhere, and let $\langle q, q' \rangle_{j,k}$ denote the tally $\langle q \rangle_j + \langle q' \rangle_k$ with $q, q' \in Q$ in the j'th and k'th positions of an otherwise-$0/0$ tally. It is to be understood that $j < k$ whenever this latter notation is used.*

Notation 2.6. *The sheer fact of having recorded a tally of the form* $\langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k}$ *means that we enrolled participants* $i, i' \in I$ *at doses* $x_j < x_k$ *respectively, and upon assessment found that:*

$$y(i, x_j) = 1,\ y(i', x_k) = 0.$$

Thus we may regard $\langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k}$ *as* ***equivalent to a proposition:***

$$\langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k} \equiv \exists\, i, i' \in I \text{ such that } y(i, x_j) = 1 \text{ and } y(i', x_k) = 0.$$

On this understanding, we can express the pharmacologic premise of ***monotone dose-toxicity*** *via,*

$$\langle \frac{1}{1} \rangle_j \implies \langle \frac{1}{1} \rangle_k \ \forall\, k > j$$

and

$$\langle \frac{0}{1} \rangle_j \implies \langle \frac{0}{1} \rangle_\ell \ \forall\, \ell < j.$$

Definition 2.7. *A preorder relation* $\leq$ *on* Q^D *is* ***dose-monotone*** *iff,*

$$\langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k} \leq \langle \frac{0}{1}, \frac{1}{1} \rangle_{j,k} \quad \forall\, j < k.$$

Notation 2.8. *Let* $\preceq_{ce}$ *denote the binary relation on* Q^D *obtained by componentwise extension of Definition 2.2,*

$$\bigwedge_{i=1}^{D} (q_i \preceq q_i') \implies q \preceq_{ce} q',$$

and let $\preceq_{dm}$ *denote the* <u>monoidal</u> *dose-monotonicity relation,*

$$q + \langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k} \preceq_{dm} q + \langle \frac{0}{1}, \frac{1}{1} \rangle_{j,k} \quad \forall\, j < k \quad \forall\, q \in Q^D, \tag{4}$$

which ensures that $+ : Q^D \times Q^D \to Q^D$ *is monotone with respect to* $\preceq_{dm}$*.*

Definition 2.9. *Let* $\mathcal{Q} = (Q^D, \preceq)$ *be the free preorder generated by* $\preceq_{ce} \cup \preceq_{dm}$*.*

Fact 2.10. *Def. 2.9 creates no ambiguity by its reuse of* $\preceq$*, since it incorporates Def. 2.2 as the special case* $D = 1$*.*

Fact 2.11. $\mathcal{Q} = (Q^D, \preceq, \langle \frac{0}{0} \rangle, +)$ *is a symmetric monoidal preorder.*

Notation 2.12. *Given a dose-indexed tuple* $x = (x_d) \in \mathbb{N}^D$*, let capitalization denote partial summation, such that* $X_d = \sum_{j=1}^{d} x_j$*, and* $X = (X_d) \in \mathbb{N}^D$*.*

Fact 2.13. *The preorder* $\preceq$ *is readily calculated from an equivalent condition,*

$$t\!:\!u \preceq t'\!:\!u' \quad \iff \quad T \geq T' \ \wedge\ U \leq U'. \tag{5}$$

Proof. It is the universal property of the free preorder $(Q^D, \preceq)$ that $\preceq$ is the reflexive, transitive closure of the relation $\preceq_{ce} \cup \preceq_{dm}$. The $(\Longleftarrow)$ direction of (5) is immediate: the RHS obviously defines a reflexive and transitive relation on $R^D \cong Q^D$, which directly implies both $\preceq_{ce}$ and $\preceq_{dm}$ as special cases. So the RHS of (5) clearly defines a preorder that contains $\preceq$.

To show the $(\Longrightarrow)$ direction, consider that any statement $q \preceq q'$ with $q \neq q'$ must arise from some finite string of the form,

$$q = q^0 \preceq_* q^1 \preceq_* \dots \preceq_* q^n = q' \quad n \geq 1, \tag{6}$$

where each $\preceq_*$ is either $\preceq_{ce}$ or $\preceq_{dm}$. But observe that across either of these $\preceq_*$'s, both $T_d^{n-1} \geq T_d^n$ and $U_d^{n-1} \leq U_d^n$ must hold $\forall d, n$. Since the latter are themselves transitive conditions, they must hold also across the whole chain from q to q'. $\square$

Corrolary 2.14. *$\preceq$ is in fact a partial order on Q^D, since $t\!:\!u \cong t'\!:\!u'$ requires both equalities on the RHS of* (5) *to hold, forcing $t_i = t'_i$ and $u_i = u'_i$ for all i.*

Notation 2.15. *Corrolary 2.14 licenses the notation $\prec$ defined by,*

$$q_1 \prec q_2 \iff q_1 \preceq q_2 \ \wedge \ q_1 \neq q_2.$$

2.1 Further characterization of the monoidal preorder $\preceq$

> Make no mistake about it: Computers process numbers — not symbols. We measure our understanding (and control) by the extent to which we can arithmetize an activity.
>
> — Alan J. Perlis (Epigram #65)

Observe that the proof of Fact 2.11 did not use the *symmetric monoidal* character of the + operation on $\mathcal{Q}$. By exploiting specifically the *commutativity* of +, however, we can obtain a more readily generalizable reformulation of (5).

Fact 2.16. *Every arrow of the preorder $\preceq$ may be obtained in the form,*

$$\sum_{i=1}^{D} \lambda_i \langle \frac{1}{1} \rangle_i + \sum_{j<k} \eta_{jk} \langle \frac{1}{1}, \frac{0}{1} \rangle_{j,k} + q \preceq q + \sum_{j<k} \eta_{jk} \langle \frac{0}{1}, \frac{1}{1} \rangle_{j,k} + \sum_{i=1}^{D} \gamma_i \langle \frac{0}{1} \rangle_i, \tag{7}$$

for some $q \in Q^D$ and $\lambda_i, \eta_{jk}, \gamma_i \in \mathbb{N}$. This is a CLP($\mathbb{Z}$) constraint.

Proof. It is clear that every statement of the form (7) is a valid arrow that we may build up by starting with the reflexive arrow $q \preceq q$, repeatedly applying $\preceq_{dm}$ (obtaining the paired η_{jk} terms), then repeatedly applying $\preceq_{ce}$; the left-hand side of (3) generates the λ_i terms, its right-hand side the γ_i terms. The converse, that all valid arrows must be of the form (7), follows from considering strings of the form (6), and exploiting the commutativity of + to collect like terms. $\square$

3 Dose-Escalation Protocols

A dose-escalation protocol (DEP) is generally situated in a queueing context, where it must service the *arrival process* of participants presenting available for enrollment. At any time, there may be 0, 1, or many participants waiting to enroll. It is the task of a dose-escalation protocol to decide at what doses (if any) to enroll the waiting participants, conditional on the trial's current state.

Definition 3.1. *A* ***cohort*** *is a pair* $(t, c) \in [0, \infty) \times \mathbb{N}^D$ *giving the number of participants enrolling concurrently at time* t *at each dose in* $\{1, ..., D\}$*. As previously for tallies, pending counts and trial states, a 'current time' will often be implicit, so that we will freely suppress the* t*-component and speak of 'cohorts' in* $\mathbb{N}^D$*.*

Definition 3.2. *Let* $\trianglelefteq$ *denote the preorder relation formed by transitive closure of the usual preorder* $\leq$ *on* $\mathbb{N}^D$*,*

$$x \leq y \implies x \trianglelefteq y \quad \forall\, x, y \in \mathbb{N}^D,$$

together with the condition

$$j \leq k \implies \widehat{j} \trianglelefteq \widehat{k} \quad \forall j, k \in \{0, ..., D\}.$$

Let $\mathcal{C} = (\mathbb{N}^D, \trianglelefteq)$ *denote the resulting preorder, and call its objects 'cohorts'. Observe that the arrows* $c \xrightarrow{\trianglelefteq} c'$ *in this category point in the direction of increasingly 'ambitious' cohorts that enroll more participants, or at higher doses.*

Notation 3.3. *Let* $\downarrow : \mathcal{C} \to 2^{\mathcal{C}}$ *denote the functor yielding the principal lower sets,*

$$\downarrow c = \{c' \in \mathcal{C} \mid c' \trianglelefteq c\}.$$

Definition 3.4. *A* ***rolling dose escalation [RDE]*** *is a functor*

$$\widetilde{E} : \mathcal{S} \to 2^{\mathcal{C}}$$

that in any trial state determines a set of admissible cohorts. The functoriality here models a caution that underlies any reasonable approach to dose escalation:

$$s \supseteq s' \implies \widetilde{E}s \subseteq \widetilde{E}s',$$

which is to say that in states with less information, enrollment options should be more restrictive.

The qualifier 'rolling' applies on account of the set-valued domain $\mathcal{S}$*, meant generally to allow for 'rolling enrollment' (cite Skolnik et al, 2008) even from plural states with pending assessments.*

The set-valued codomain of $\widetilde{E}$ *is intended to allow generally for servicing waiting queues of different sizes, and even for the arbitrary exercise of 'clinical judgment' in dose assignments.*

We will freely regard any functor $\widetilde{E} : \mathcal{S} \to \mathcal{C}$ *as the RDE,* $\downarrow \circ \widetilde{E} : \mathcal{S} \to 2^{\mathcal{C}}$*.*

The high generality of Definition 3.4 allows for development of a taxonomy that identifies and names various desirable properties which, at their intersection, may define a class of rational DEP's of practical interest. But we now leap ahead to a highly restrictive class, in order to make concrete progress.

Notation 3.5. *For $D \in \mathbb{N}^{+}$, let $\mathcal{D}$ denote the preorder consisting of the set $\{0, 1, ..., D\}$ equipped with the (reflexive and transitive) relation $\leq$ defined as usual on $\mathbb{N}$. In order to use categorical language, we will regard $\mathcal{D}$ as the category freely generated by the graph, $0 \to 1 \to \cdots \to D$.*[3]

Definition 3.6. *An **incremental enrollment [IE]** is a functor $\mathcal{Q} \xrightarrow{E} \mathcal{D}$. Note that the functoriality here imposes the core intuition of dose-escalation,*

$$q \preceq q' \implies Eq \leq Eq',$$

that dose assignment should correlate with evident safety.

Notation 3.7. *Let $\mathcal{S} \xrightarrow{\bigwedge} \mathcal{Q}$ denote the functor defined by the worst-possible (most toxic) resolution,*

$$\bigwedge s = \bigwedge_{q \in s} q.$$

The right-hand side is well-defined, since any given state s is finite, and $\mathcal{Q}$ is a strict preorder (i.e., partial order) by Corollary 2.14. Functoriality holds because $s \supseteq s' \implies \bigwedge_{q\in s} q \preceq \bigwedge_{q \in s'} q$.

Notation 3.8. *Let $\mathcal{D} \xrightarrow{\widehat{-}} \mathcal{C}$ be the functor defined by $\widehat{d} = ([j = d])_{j \in \mathcal{D}}$, where $[-]$ represents the Iverson bracket,*

$$[P] = \begin{cases} 1 & \text{if } P \text{ is true} \\ 0 & \text{otherwise.} \end{cases}$$

Thus, $\widehat{0}$ is a D-vector of all zeros, and for $d > 0$, $\widehat{d}$ is the vector $(0, ..., 0, 1, 0, ..., 0)$ with 1 in the d'th position. The functoriality of $\widehat{-}$ arises directly from the 2nd condition in Definition 3.2.

Notation 3.9. *Given IE $\mathcal{Q} \xrightarrow{E} \mathcal{D}$, define $\widehat{E} = \widehat{-} \circ E \circ \bigwedge$:*

$$\begin{tikzcd}
\mathcal{Q} \arrow[r, "E"] & \mathcal{D} \arrow[d, "\widehat{-}"] \\
\mathcal{S} \arrow[u, "\bigwedge"] \arrow[r, "\widehat{E}"'] & \mathcal{C}
\end{tikzcd}$$

[3]More conventionally, the ordinal category with D+1 elements would be written $\mathbb{D} + \mathbb{1}$; see Riehl Example 4.1.14. But we trust no confusion will arise from our notation $\mathcal{D}$.

Fact 3.10. *'E' and '$\bigwedge$' commute in the definition of $\widehat{E}$:*

$$\widehat{E}s = E\left(\bigwedge s\right) = E\bigwedge_{q\in s} q = \bigwedge_{q\in s} Eq.$$

Notation 3.11. *Given IE $\mathcal{Q} \xrightarrow{E} \mathcal{D}$, define functors $\mathcal{S} \xrightarrow{\widehat{E}_n} \mathcal{S}, n \in \mathbb{N}$ by,*

$$\begin{aligned}\widehat{E}_0 s &= s\\ \widehat{E}_{n+1} s &= \widehat{E}_n s \oplus \sqrt{\widehat{E}}(\widehat{E}_n s).\end{aligned}$$

Fact 3.12. *Given a state $s \in \mathcal{S}$, the sequence $(\widehat{E}_n s)_{n\in\mathbb{N}}$ defines a diagram in $\mathcal{S}$ of shape $(\mathbb{N}, \leq)^{\mathrm{op}}$:*

$$\cdots \supseteq \widehat{E}_2 s \supseteq \widehat{E}_1 s \supseteq \widehat{E}_0 s \equiv s,$$

for which the so-called 'inverse limit' is $\varprojlim \widehat{E}_- s = \bigcup_{n\in\mathbb{N}} \widehat{E}_n s$.[4]

Notation 3.13. *Let $\widehat{E}_\leftarrow : \mathcal{S} \to \mathcal{S}$ denote the functor defined by these limits,*

$$\widehat{E}_\leftarrow s = \varprojlim \widehat{E}_- s = \bigcup_{n\in\mathbb{N}} \widehat{E}_n s.$$

Definition 3.14. *The **RDE generated by an IE** $\mathcal{Q} \xrightarrow{E} \mathcal{D}$ is the functor $\widetilde{E} : \mathcal{S} \to \mathcal{C}$ defined by the equation,*

$$\widehat{E}_\leftarrow s = s \oplus \sqrt{\widetilde{E}} s.$$

$$\begin{tikzcd}
\mathcal{S} \arrow[rr, bend left, "\sqrt{\widetilde{E}}"] \arrow[dr, "\widehat{E}_\leftarrow"'] & \mathcal{S}\times\mathcal{A} \arrow[l, "\pi_{\mathcal{S}}"'] \arrow[r, "\pi_{\mathcal{A}}"'] \arrow[d, "\oplus"] & \mathcal{A} \\
& \mathcal{S} &
\end{tikzcd}$$

3.1 A Concrete Construction

In this subsection, we motivate and elucidate the rather abstract Definition 3.14 using a more concrete construction.

Notation 3.15. *Given IE $\mathcal{Q} \xrightarrow{E} \mathcal{D}$ and a tally $q \in \mathcal{Q}$, define sequences $e_n(q) \in \{0, ..., D\}$ and $E_n(q) \in S$ inductively by the mutually recursive relations,*

$$\begin{aligned}e_1(q) &= Eq\\ E_n(q) &= q \oplus \sqrt{\sum_{k=1}^{n} \widehat{e_k(q)}}\\ e_{n+1}(q) &= \bigwedge_{q'\in E_n(q)} Eq'.\end{aligned}$$

[4]Leinster [Ex. 5.1.21(d), p.120] seems to disparage the term 'inverse' as "old fashioned", whereas Riehl [Def. 3.1.21, p.80] presents it as standard.

This defines how, from the standpoint of a singular trial state $q \oplus \{\widehat{0}\} \in \mathcal{S}$, one might proceed to enroll participants from a waiting queue: enroll a first participant at dose $\mathrm{e}_1(q)$; then, from the standpoint of the resulting plural state $E_1(q) = q \oplus \sqrt{\widehat{\mathrm{e}_1(q)}}$, the minimax principle suggests $\mathrm{e}_2(q) = \bigwedge_{q' \in E_1(q)} Eq'$ as a suitable dose for enrolling a second participant; this yields the even larger state $E_2(q)$, which may then admit further enrollment, and so on.

Fact 3.16. *The sequence $(e_n(q))_{n \in \mathbb{N}^+}$ is nonincreasing:*

$$m < n \implies e_m(q) \geq e_n(q) \quad \forall\, q \in \mathcal{Q}.$$

Fact 3.17. *The sequence $(E_n(q))_{n \in \mathbb{N}^+}$ is nested:*

$$m < n \implies E_m(q) \subseteq E_n(q) \quad \forall\, q \in \mathcal{Q}.$$

Except in pathological cases (**TODO:** rule these out by some explicit provision), the sequence $e_n(q)$ must become zero after a finite number of terms, at which point the sequence $E_n(q)$ converges.

3.2 A Categorical Perspective

The construction in Notation 3.15 can be appreciated via cones over and under the diagram $(\mathbb{N}, \leq)^{\mathrm{op}} \xrightarrow{E_{-}s} \mathcal{S}$, with summit $a \in \mathcal{S}$ and nadir $s = q \oplus \{\widehat{0}\}$:

$$\begin{tikzcd}
a \arrow[d, "\supseteq"] \arrow[dr, "\supseteq"] \arrow[drr, "\supseteq"] \arrow[drrr, "\supseteq"] & & & \\
\dots \arrow[r, "\supseteq"] \arrow[d, "\subseteq"] & E_2 s \arrow[r, "\supseteq"] \arrow[dl, "\subseteq"] & E_1 s \arrow[r, "\supseteq"] \arrow[dll, "\subseteq"] & E_0 s \equiv s \arrow[dlll, "\subseteq"] \\
s & & &
\end{tikzcd}$$

This reveals Definition 3.14 as a limit,

$$E^*(s) = \varprojlim E_n s,$$

the limit cone being

$$\begin{tikzcd}
\varprojlim E_n s \arrow[d, "\supseteq"] \arrow[dr, "\supseteq"] \arrow[drr, "\supseteq"] \arrow[drrr, "\supseteq"] & & & \\
\dots \arrow[r, "\supseteq"] & E_2 s \arrow[r, "\supseteq"] & E_1 s \arrow[r, "\subseteq"] & E_0 s \equiv s,
\end{tikzcd}$$

with projections $E^*(s) \supseteq E_n s$ defining admissible cohorts of size n.

4 Conjectures

Conjecture 4.1. *Many standard dose-escalation protocols, including 3 + 3 and BOIN designs, will give rise implicitly to an enlargement of the preorder* $(Q^D, \preceq)$ *of Definition 2.9. This preorder, in turn, will define uniquely a dose-monotone 'correction' of the original protocol.*

4.1 Rectification of the 3+3 trial design

Let us examine Conjecture 4.1 in the context of the 3+3 trial. The smallest nontrivial 3+3 design considers $D = 2$ doses, and has 46 possible paths [1]. These paths terminate in 29 distinct tallies, each with a dose-level recommendation in $\{0, 1, 2\}$ defined by the protocol.

```
:- use_module(rcpearl). % Predicates defined in Norris & Triska (2024)
:- use_module(library(lists)).
:- use_module(library(dcgs)).
:- use_module(library(lambda)).
:- use_module(library(format)).
:- use_module(library(tabling)).

:- table endtally_rec/2.
endtally_rec(FinalTally, Rec) :-
    phrase(path([0/0]-[0/0]), Path),
    phrase((..., [Endstate,stop,recommend_dose(Rec)]), Path),
    state_tallies(Endstate, FinalTally).

?- N+\(setof(Q-Rec, endtally_rec(Q, Rec), QRecs),
       maplist(portray_clause, QRecs), length(QRecs, N)).
% Output is verbatim, but reordered and tabulated for display:
%@ [2/3,0/0]-0.   %@ [0/6,2/3]-1.   %@ [0/3,0/6]-2.
%@ [2/6,0/0]-0.   %@ [0/6,2/6]-1.   %@ [0/3,1/6]-2.
%@ [2/6,2/3]-0.   %@ [0/6,3/3]-1.   %@ [1/6,0/6]-2.
%@ [2/6,2/6]-0.   %@ [0/6,3/6]-1.   %@ [1/6,1/6]-2.
%@ [2/6,3/3]-0.   %@ [0/6,4/6]-1.
%@ [2/6,3/6]-0.   %@ [1/6,2/3]-1.
%@ [2/6,4/6]-0.   %@ [1/6,2/6]-1.
%@ [3/3,0/0]-0.   %@ [1/6,3/3]-1.
%@ [3/6,0/0]-0.   %@ [1/6,3/6]-1.
%@ [3/6,2/3]-0.   %@ [1/6,4/6]-1.
%@ [3/6,2/6]-0.
%@ [3/6,3/3]-0.
%@ [3/6,3/6]-0.
%@ [3/6,4/6]-0.
%@ [4/6,0/0]-0.
%@    N = 29.
```

Thus, the 3+3 trial yields a mapping from a (29-element) subset of Q^2 to $\{0, 1, 2\}$. In light of the foregoing, it is natural at this point to ask whether we might extend this mapping to an incremental enrollment $\mathcal{Q} \xrightarrow{E} \mathcal{D}$. To be amenable to such extension, these dose recommendations would have to be *functorial*, so let us check for any violation of functoriality. Any such violation must take the form of final tallies $q_1, q_2 \in Q^2$ with associated dose-level recommendations $d_1, d_2 \in 0, 1, 2$ such that $q_1 \preceq q_2$ but $d_1 \not\leq d_2$:

```
?- endtally_rec(Q1, D1),
   endtally_rec(Q2, D2),
   Q1 '⪯' Q2, % Q1 evidently no safer than Q2,
   D1 #>  D2. % yet recommended D1 exceeds D2.
%@    Q1 = [1/6,1/6], D1 = 2, Q2 = [0/6,2/6], D2 = 1
%@ ;  false.
```

Thus, interestingly, we discover that the dose recommendations of the 3+3 trial are not actually consistent with the basic pharmacologic intuition embodied in our dose-monotonicity condition of Definition 2.7: substituting $q = (\frac{0}{5}, \frac{1}{5})$ into Equation (4), we see that $(\frac{1}{6}, \frac{1}{6}) \preceq (\frac{0}{6}, \frac{2}{6})$, yet the 3+3 design accords the *higher* dose to the *less safe* of the two tallies. Adapting existing dose-escalation designs to the framework presented here will generally require an initial 'rectification' step, in which nonmonotonicities implicit in existing designs are corrected.

```
table mendtally_rec/2.
mendtally_rec(Q, D) :- mendtally_rec(Q, D, _).

mendtally_rec(Q, D, Ds) :-
    endtally_rec(Q, D0),
    findall(Di, (endtally_rec(Qi, Di),
                 Q ⪯ Qi,    % Q is no safer than Qi,
                 D0 #> Di), % yet its rec exceeds Di.
            Ds),
    foldl(clpz:min_, Ds, D0, D).

?- mendtally_rec(Q, D, [_|_]).
%@    Q = [1/6,1/6], D = 1 % the sole rectification needed
%@ ;  false.

?- mendtally_rec(Q1, D1),
   mendtally_rec(Q2, D2),
   Q1 ⪯ Q2,
   D1 #> D2.
%@    false. % Rectification succeeded.
```

With the aim of extracting as much information as possible from existing designs, one might suppose it useful to consider not only *final* tallies with their dose recommendations, but also *interim* tallies and their associated *next*-dose recommendations. But because the latter may be entangled with considerations of trial *progress*, they seem less readily interpretable as expressing the design's underlying pharmacologic intuitions.

4.2 Extending the dose-recommendation functor to an IE

Rectification has yielded a final dose recommendation,

$$\mathcal{Q}_f \xrightarrow{F} \mathcal{D} \equiv \{0 \leq 1 \leq 2\},$$

that is *functorial* on the preorder of final tallies $\mathcal{Q}_f \subset \mathcal{Q}$. If we could extend F along the inclusion $\mathcal{Q}_f \overset{\iota}{\hookrightarrow} \mathcal{Q}$ to a functor $\mathcal{Q} \xrightarrow{E} \mathcal{D}$, then we would obtain an incremental enrollment (IE) consistent with the 3+3 design.

$$\begin{tikzcd}
\mathcal{Q} \arrow[r, dashed, "E?"] & \mathcal{D} \\
\mathcal{Q}_f \arrow[u, "\iota"] \arrow[ur, "F"'] &
\end{tikzcd}$$

Since many such extensions will generally exist, we may wish to focus on finding simple or otherwise optimal solutions. One especially appealing form of enrollment would be one with an adjoint:

Definition 4.2. *A* ***Galois enrollment*** *is an IE $\mathcal{Q} \xrightarrow{E} \mathcal{D}$ for which* <u>*either*</u> *a right (upper) or left (lower) adjoint exists:*

$$\begin{tikzcd}
\mathcal{Q}^* \arrow[rr, "E"] & \arrow[phantom, "\top"] & \mathcal{D} \arrow[ll, bend right, "G"']
\end{tikzcd}$$

or

$$\begin{tikzcd}
\mathcal{Q}^* \arrow[rr, "E"] & \arrow[phantom, "\top"] & \mathcal{D} \arrow[ll, bend left, "L"]
\end{tikzcd},$$

and where $\mathcal{Q}^* = (Q^D, \preceq^*, \langle {0 \atop 0} \rangle, +)$ represents generally an enlargement of the basic preorder $\mathcal{Q}$, with $\preceq \subset \preceq^*$. (An adjunction between preorders is called a Galois connection, hence the name; see Reihl p118 and Fong & Spivak Definition 1.90, p27.)

The appeal of a Galois enrollment is that it effectively embeds much of the enrollment protocol in the preorder $\preceq^*$. In the case of a lower Galois enrollment $E \dashv G$, the upper adjoint G provides the rule,

$$E(q) \leq d \quad \iff \quad q \preceq^* G(d),$$

and for an upper Galois enrollment $L \dashv E$ we have,

$$d \leq E(q) \quad \iff \quad L(d) \preceq^* q.$$

Writing $G(d) = g_d$, we thus obtain $\{g_0, ..., g_D\} \subset \mathcal{Q}$ that partition $\mathcal{Q}$ in a bottom-up cascade, with $q \preceq^* g_0 \implies E(q) = 0$, else $q \preceq^* g_1 \implies E(q) = 1$, and so forth. Similarly, $\{\ell_d = L(d)\} \subset \mathcal{Q}$ would generate a top-down cascade.

A lower Galois enrollment for our 2-dose 3+3 trial would then be determined by a tuple $(g_0, g_1, g_2) \in Q^{D+1}$ together with some enlargement $\preceq^*$ of the basic preorder. Indeed, since g_2 could be set to be some very safe tally such as $(\frac{0}{6}, \frac{0}{6})$ that would serve as a 'catchall' in our cascade, the only nontrivial search is then for $(g_0, g_1) \in Q^D$. Although we do not (yet) have a suitably enlarged $\preceq^*$ in hand, the implication $q \preceq q' \implies q \preceq^* q'$ nevertheless does allow us to write down some constraints on the g_d. Specifically, any candidate g_d must satisfy,

$$q \preceq g_d \implies q \preceq^* g_d \implies E(q) \leq d \implies F(q) \leq d \quad \forall q \in \mathcal{Q}_f, \tag{8}$$

in which the first implication follows from $\preceq \subseteq \preceq^*$, the second from assuming that E is lower-Galois, and the third from assuming that E extends F. Furthermore, if we are looking for *best* candidate g_0 and g_1, then we would like these to be safest-possible tallies satisfying (8).

References

[1] David C. Norris and Markus Triska. An Executable Specification of Oncology Dose-Escalation Protocols with Prolog, February 2024. arXiv:2402.08334 [cs].