DRAFT: A Categorical Formulation of Dose-Escalation Designs

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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 $(2^X)^{\mathrm{op}}$ is then the preorder $(2^X, \supseteq)$.*

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

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.

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

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:

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

□

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:***

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

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'. □

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. □

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,*

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

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 $e_1(q)$; then, from the standpoint of the resulting plural state $E_1(q) = q \oplus \widehat{\sqrt{e_1(q)}}$, the minimax principle suggests $e_2(q) = \bigwedge_{q' \in E_1(q)} Eq'$ 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 $s = q \oplus \{\widehat{0}\}$:

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

This reveals Definition 3.14 as a limit,

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

the limit cone being

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

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 non-trivial 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. A cautious approach to such rectification in this case might simply assign the dose recommendation of $D = 1$ to the tally $(\frac{1}{6}, \frac{1}{6})$.

Generally, we will want to extract as much information as possible from existing designs, and to this end we may consider not only *final* tallies with their dose recommendations, but also *interim* tallies and their associated next-dose recommendations. In the 3+3 trial, there are a total of ...

Definition 4.2. *A **Galois enrollment** $L \dashv E \dashv F$ is an IE $\mathcal{Q} \xrightarrow{E} \mathcal{D}$ for which both left (lower) and right (upper) adjoints L and F exist:*

$$\begin{tikzcd} \mathcal{Q} \arrow[r, "E" description] \arrow[r, phantom, shift left=3, "\top"] \arrow[r, phantom, shift right=3, "\top"] & \mathcal{D} \arrow[l, bend right=40, "F"'] \arrow[l, bend left=40, "L"] \end{tikzcd}$$

(The name is suggested by the fact that an adjunction between preorders is called a Galois connection. See Reihl p118 and Fong & Spivak Definition 1.90, p27.)

Conjecture 4.3. *A Galois enrollment is too much to hope for, since it implies*

$$E^{-1}d = \{q \mid L\,d \preceq q \preceq F d\}.$$

But if this conjecture is wrong, we need to know! If such IE's were available generally or even widely, they would have strong properties worth understanding.

References

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