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 $t \le n$ 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 $Q = \{t/n \mid t, n \in \mathbb{N}; t \le n\}$ 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

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

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,*

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

of all its possible resolutions. The surd notation $\surd$ *is meant to convey the idea that* $\sqrt{p}$ *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* $(\sqrt{p})_d \subset Q \subset \mathbb{N}^2$. *Pronouncing* $\surd$ *'res' instead of 'root' in this context may help.*

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

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

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

To see this, simply consider any resolution in $\sqrt{p}$ *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,

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

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

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

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

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

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

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 $0 \oplus -$:*

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

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

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

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

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 $S^* = \surd S \cup \{\emptyset, U\}$ is closed under set intersections. This is readily appreciated from the geometry of the components $(\surd s \cap \surd s')_d$ 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 $\{s \cap U \mid s \in \surd S\}$. 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* $(\frac{0}{0}, \ldots, \frac{0}{0})$*.*

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:

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

□

Notation 2.5. *Let* $\langle q \rangle_j$ *denote the tally* $(\frac{0}{0}, \ldots, \frac{0}{0}, q, \frac{0}{0}, \ldots, \frac{0}{0}) \in Q^D$ *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,*

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

and

$$\langle \frac{0}{1} \rangle_j \impliedby \langle \frac{0}{1} \rangle_k \;\forall\, j < k.$$

Definition 2.7. *We call a monoidal preorder relation* $\leq$ *on* Q^D ***dose-monotone*** *iff it contains the following arrows* $\forall j \in \{1, ..., D-1\}$*:*

$$\begin{gathered}
\langle \frac{0}{0} \rangle \preceq_{tol_1} \langle \frac{0}{1} \rangle_1 \\
\langle \frac{0}{1} \rangle_j \preceq_{titr_j} \langle \frac{0}{1} \rangle_{j+1} \\
\langle \frac{1}{2} \rangle_D \preceq_{1:1} \langle \frac{0}{0} \rangle \\
\langle \frac{1}{1}, \frac{0}{1} \rangle_{j,j+1} \preceq_{exch_j} \langle \frac{0}{1}, \frac{1}{1} \rangle_{j,j+1}
\end{gathered}$$

The subscripts on $\preceq_*$ in Definition 2.7 indicate the underlying intuition of these 'atomic' arrows, considered as incremental transformations which tallies may undergo as a trial progresses. Thus, observing a new participant's toleration of dose 1 yields a new tally that is evidently safer:

$$q \preceq_{tol_1} q + \langle \frac{0}{1} \rangle_1.$$

Likewise, the transformation corresponding to $\preceq_{titr}$ would be one in which a trial participant who has tolerated dose j subsquently titrates upward to $j+1$ and tolerates this dose as well. That dose-escalation designs exclude such titration maneuvers by definition[3] does not exempt them from the underlying pharmacological principle expressed in $\preceq_{titr}$. Thus, we are entitled to examine dose-escalation trials in light of this principle, even if their designs do not explicitly acknowledge it. (If one wished to interpret $\preceq_{titr}$ strictly in the narrowed ontology of dose-escalation designs, this could be done by adopting a potential-outcomes framing.)

[3] I am appealing here an escalation–titration distinction introduced in [1] with some support from the treatment of these issues in e.g. [2].

The $\preceq_{1:1}$ arrows serve to break a symmetry that would otherwise exist between observed toxicity and tolerability. They state that observed in a $1:1$ ratio at the highest dose, toxicity and non-toxicity on balance yield a less safe tally. Intuitively, we might understand these judgments as establishing a prior expectation of toxicity rate below 0.5 *even at the highest dose*, so that the derogatory informational content (entropy) of a toxicity outweighs the favorable information of a non-toxicity.

Similar considerations help us to understand $\preceq_{exch}$ as likewise breaking a symmetry between toxicity and tolerability, albeit now *across two distinct doses*. To see this, consider the notationally convenient case $D = 2$. Suppose we sample pairs (i, i') of individuals from a population with a continuously distributed latent toxicity threshold, assigning i to dose 1 and i' to dose 2. Then observing $(\mathtt{x}, \mathtt{o})$ means that individual i experienced toxicity at dose 1 while i' tolerated dose 2. Due to the monotonicity of dose-response, we then know that (counterfactually) had we sampled these individuals in the opposite order (i', i), we would have observed $(\mathtt{o}, \mathtt{x})$. Thus each observed $(\mathtt{x}, \mathtt{o})$ points to *an ensemble of potential samples* in which $(\mathtt{x}, \mathtt{o})$ and $(\mathtt{o}, \mathtt{x})$ observations match one-to-one. But crucially, no such implication arises in the opposite direction, from an observation of $(\mathtt{o}, \mathtt{x})$. Consequently, there is a sense in which

$$(\mathtt{x}, \mathtt{o}) \implies (\mathtt{o}, \mathtt{x}),$$

so that we may say $(\mathtt{x}, \mathtt{o})$ has *higher information content* than $(\mathtt{o}, \mathtt{x})$. Moreover, according the principle established by $\preceq_{1:1}$, both $(\mathtt{x}, \mathtt{o})$ and $(\mathtt{o}, \mathtt{x})$ have net *derogatory* content regarding evident safety. Thus, $(\mathtt{x}, \mathtt{o})$ is the *more derogatory* of the two:

$$\langle \frac{1}{1}, \frac{0}{1} \rangle \preceq_{exch} \langle \frac{0}{1}, \frac{1}{1} \rangle.$$

Notation 2.8. *For $r \in \mathbb{N}$, let $\preceq_{1:r}$ denote the monoidal arrows generated by,*

$$\langle \frac{1}{1+r} \rangle_D \preceq_{1:r} \langle \frac{0}{0} \rangle.$$

Fact 2.9. *Given $\preceq_{tol_1}$ and $\preceq_{titr}$, we have $q \preceq_{1:r} q' \implies q \preceq_{1:1} q'$.*

Proof. By recursion on r:

$$\langle \frac{0}{0}, ..., \frac{1}{r} \rangle \preceq_{tol_1} \langle \frac{0}{1}, ..., \frac{1}{r} \rangle (\preceq_{titr})^D \langle \frac{0}{0}, ..., \frac{1}{1+r} \rangle \preceq_{1:r} \langle \frac{0}{0} \rangle.$$

□

Definition 2.10. *Let $\mathcal{Q}_r = (Q^D, \preceq_r)$ denote the monoidal preorder generated by the atomic arrows $\preceq_{ce} \cup \preceq_{dm}$.*

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

Fact 2.12. *The $(\mathcal{Q}_r)_{r \in \mathbb{N}}$ form a nested sequence of subcategories, $\mathcal{Q}_r \hookrightarrow \mathcal{Q}_{r+1}$.*

2.1 An explicit characterization of $\preceq_r$

Notation 2.13. *Interpreting $\preceq_{tol_1}$ as 'titration upward from dose 0', we will write $\preceq_{titr_0}$ in its place. Thus, we obtain a sequence $(\preceq_{titr_j})_{0\leq j<D}$ of D atomic titration arrows with zero-based indexing.*

Theorem 2.14. *Each arrow $q \preceq_r q'$ of $\mathcal{Q}_r$ has a unique expression in the form,*

$$q\ (\preceq_{exch_{12}})^{\gamma_1} ... (\preceq_{exch_{D-1,D}})^{\gamma_{D-1}} (\preceq_{1:r})^{\gamma_D} (\preceq_{titr_0})^{\eta_0} ... (\preceq_{titr_{D-1}})^{\eta_{D-1}}\ q', \tag{4}$$

for a vector $(\gamma, \eta) = (\gamma_1, ..., \gamma_D, \eta_0, ..., \eta_{D-1}) \in \mathbb{N}^{2D}$.

Proof. (D = 3 case.) Take $q = (t\,{:}\,u) \preceq_r (t'\,{:}\,u') = q'$, and write

$$\begin{aligned} t' - t &= \Delta t = (\Delta t_1, \Delta t_2, \Delta t_3), \\ u' - u &= \Delta u = (\Delta u_1, \Delta u_2, \Delta u_3). \end{aligned} \tag{5}$$

Now multiplying (row-vector) (γ, η) on the *right* by the 6×6 matrix,

$$\begin{array}{cc|cccccc}
 & & \Delta t_1 & \Delta t_2 & \Delta t_3 & \Delta u_1 & \Delta u_2 & \Delta u_3 \\
(\preceq_{exch_{12}}) & \gamma_1 & -1 & +1 & & +1 & -1 & \\
(\preceq_{exch_{23}}) & \gamma_2 & & -1 & +1 & & +1 & -1 \\
(\preceq_{1:r}) & \gamma_3 & & & -1 & & & -r \\
(\preceq_{titr_0}) & \eta_0 & & & & +1 & & \\
(\preceq_{titr_1}) & \eta_1 & & & & -1 & +1 & \\
(\preceq_{titr_2}) & \eta_2 & & & & & -1 & +1
\end{array}$$

yields the vector $(\Delta t, \Delta u)$. Since this matrix is invertible over $\mathbb{Z}$,

$$\begin{pmatrix} -1 & +1 & & +1 & -1 & \\ & -1 & +1 & & +1 & -1 \\ & & -1 & & & -r \\ & & & +1 & & \\ & & & -1 & +1 & \\ & & & & -1 & +1 \end{pmatrix}^{-1} = \begin{pmatrix} -1 & -1 & -1 & -r & -r-1 & -r-1 \\ & -1 & -1 & -r & -r & -r-1 \\ & & -1 & -r & -r & -r \\ & & & 1 & & \\ & & & 1 & 1 & \\ & & & 1 & 1 & 1 \end{pmatrix},$$

we obtain a 1-1 correspondence between formal differences $q' - q = (\Delta t, \Delta u)$ and 'arrow coefficients' $(\gamma, \eta) \in \mathbb{Z}^6$ such that the arrows $q \preceq_r q'$ correspond to exactly those cases where these coefficients are all non-negative. $\square$

Corrolary 2.15. *$\preceq_r$ is in fact a <u>partial order</u> on Q^D, since $q \cong q'$ requires both (γ, η) and $(-\gamma, -\eta)$ to be non-negative, which can hold only if $\gamma = \eta = 0$, whence $\Delta t = \Delta u = 0$ and thus $q = q'$.*

Notation 2.16. *Corrolary 2.15 licenses the notation $\prec$ defined by,*

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

Fact 2.17. $\langle \genfrac{}{}{0pt}{}{0}{0} \rangle \preceq_r \langle \genfrac{}{}{0pt}{}{0}{1} \rangle_d\ \forall d \in 1..D.$

Proof. Using Notation 2.13, we can write

$$\langle \frac{0}{0} \rangle \preceq_{titr_0} \langle \frac{0}{1} \rangle_1 \preceq_{titr_1} \cdots \preceq_{titr_{d-1}} \langle \frac{0}{1} \rangle_d .$$

$\square$

Fact 2.18. $\langle \frac{1}{2} \rangle_d \preceq_r \langle \frac{0}{0} \rangle \; \forall d \in 1..D.$

Proof. From $\langle \frac{1}{2} \rangle_D \preceq_{1:1} \langle \frac{0}{0} \rangle$, we proceed by induction on $d < D$:

$$\langle \frac{1}{2} \rangle_d \preceq_{titr_d} \langle \frac{1}{1}, \frac{0}{1} \rangle_{d,d+1} \preceq_{exch_d} \langle \frac{0}{1}, \frac{1}{1} \rangle_{d,d+1} \preceq_{titr_d} \langle \frac{1}{2} \rangle_{d+1} .$$

$\square$

Fact 2.19. $\langle \frac{1}{1} \rangle_d \preceq_r \langle \frac{0}{0} \rangle \; \forall d \in 1..D.$

Proof.

$$\langle \frac{1}{1} \rangle_d \preceq_{\text{Fact 2.17}} \langle \frac{1}{2} \rangle_d \preceq_{\text{Fact 2.18}} \langle \frac{0}{0} \rangle .$$

$\square$

Facts 2.17 and 2.19 reassure us that Definition 2.7 suffices to obtain intuitively necessary evident-safety relations, such that each new observation of tolerability at any dose yields a safer tally, and each new observation of a toxicity yields a less-safe tally. Note also how Facts 2.17 and 2.18 have the similar effect of showing that the 'edge-case' arrows $\preceq_{tol_1}$ and $\preceq_{1:1}$ of Definition 2.7 apply not just at $d = 1$ and $d = D$, respectively, but at all doses.

Notation 2.20. *For any* $q = (\frac{t_d}{n_d})_{d \in 1..D} \in \mathcal{Q}$*, define* $|q| = \max_{d \in 1..D} n_d$.

Lemma 2.21. *For any* $q \in \mathcal{Q}_r$*, there exist* $q_0, q_1 \in \mathcal{Q}$ *such that* $q_0 \prec_r q \prec_r q_1$.

Proof. For $n > |q|$, set $q_0 = (\frac{n}{n}, ..., \frac{n}{n})$, $q_1 = (\frac{0}{n}, ..., \frac{0}{n})$, then whittle these down to q by repeated, componentwise application of Facts 2.19 and 2.17. $\square$

Fact 2.22. *For* $D > 1$*,* $\mathcal{Q}_r$ *does* <u>*not*</u> *in general have all meets.*

Proof. Take the $D = 2, r = 2$ case. Then for $q = (\frac{1}{1}, \frac{0}{1})$ and $q' = (\frac{0}{0}, \frac{1}{1})$ we have arrows

$$(\frac{1}{1}, \frac{1}{1}) \xrightarrow[\preceq_2]{(\gamma,\eta)} q \quad \text{and} \quad (\frac{1}{1}, \frac{1}{1}) \xrightarrow[\preceq_2]{(\gamma',\eta')} q'$$

with $(\gamma, \eta) = (0, 1, 3, 3)$ and $(\gamma', \eta') = (1, 1, 2, 3)$. Now if the meet $q \wedge q'$ *did* exist, then we would have

$$(\frac{1}{1}, \frac{1}{1}) \xrightarrow[\preceq_2]{(\gamma\wedge\gamma',\eta\wedge\eta')} (q \wedge q').$$

But as it turns out this computation yields the *invalid* tally $(\frac{1}{0}, \frac{0}{1}) \notin \mathcal{Q}$. $\square$

Conjecture 2.23. $\mathcal{Q}_r$ *is however an* <u>*upper semilattice*</u>*, since it has all joins.*

Sketch of proof. Given $q, q' \in \mathcal{Q}$, choose a referent $\bar{q} = (\frac{0}{\bar{u}_1}, ..., \frac{0}{\bar{u}_D})$ such that $q, q' \preceq \bar{q}$. Regardless of how $(\bar{u}_d)_{d=1}^D$ are chosen, both γ and γ' will be nonnegative, *nondecreasing* vectors:

$$0 \leq \gamma_1 \leq ... \leq \gamma_D \quad \text{and} \quad 0 \leq \gamma'_1 \leq ... \leq \gamma'_D,$$

so that $\gamma \vee \gamma'$ will have this same property. Since $\gamma_d = \sum_{i=1}^d t_i$ (cf. the upper, left block of the matrix inverse in the proof of Theorem 2.14), we are assured of non-negative toxicity counts in $q \vee q'$.

Now provided that the $(\bar{u}_d)$ of $\bar{q}$ are chosen so that in

$$q \xrightarrow[\preceq_r]{(\gamma,\eta)} \bar{q} \quad \text{and} \quad q' \xrightarrow[\preceq_r]{(\gamma',\eta')} \bar{q}$$

at least one of $\{\eta_d, \eta'_d\}$ is zero for each $d \in 1..D$, then we then have $\eta \vee \eta' = 0$, and a similar guarantee of non-negativity for the tolerance counts in $q \vee q'$. ■

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 $\downarrow\colon \mathcal{C} \to 2^{\mathcal{C}}$ 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, $0 \to 1 \to \cdots \to D$.*[4]

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 lattice. Functoriality holds because $s \supseteq s' \implies \bigwedge_{q \in s} q \preceq \bigwedge_{q \in s'} q$.

[4]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 $\mathcal{D}$.

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 $\widehat{E} = \widehat{-} \circ E \circ \bigwedge$:*

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

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,*

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

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 $\varprojlim \widehat{E}_- s = \bigcup_{n\in\mathbb{N}} \widehat{E}_n s$.[5]

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,*

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

[5] 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.

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

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,*

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

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 $E_1(q) = q \oplus \sqrt{\widehat{e_1(q)}}$, 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 $s = q \oplus \{\widehat{0}\}$:

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

This reveals Definition 3.14 as a limit,

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

the limit cone being

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

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

4 Extensions of standard protocols

Conjecture 4.1. *Many standard dose-escalation protocols, including 3 + 3 and BOIN designs, will extend to RDEs generated by IEs. Solutions to this extension problem will generally be neither unique nor exact, and our approximate solutions may involve 'corrections' 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 [3]. 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 defines a *partial* function $Q^2 \overset{F}{\rightharpoonup} \{0, 1, 2\}$ that maps a subset $|\mathcal{Q}_f| \subset Q^2$ of 29 final tallies to their respective dose recommendations. In view of Conjecture 4.1, we would like to pose and solve the extension problem,

$$\begin{tikzcd}
\mathcal{Q}_f \arrow[rr, "F"] \arrow[dr, hook, "\iota"'] & & \mathcal{D} \\
& \mathcal{Q} \arrow[ur, dashed, "E?"'] &
\end{tikzcd} \tag{6}$$

The subcategory inclusion $Q_f \overset{\iota}{\hookrightarrow} \mathcal{Q}_f$ is of course functorial, but what about F? Any violation of functoriality by F must take the form of final tallies $q_1, q_2 \in \mathcal{Q}_f$ with respective 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: we see indeed that

$$(\frac{1}{6}, \frac{1}{6}) = (\frac{0}{5}, \frac{1}{5}) + (\frac{1}{1}, \frac{0}{1}) \preceq_{exch_{12}} (\frac{0}{1}, \frac{1}{1}) + (\frac{0}{5}, \frac{1}{5}) = (\frac{0}{6}, \frac{2}{6}),$$

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 $\mathcal{Q}_f \subset \mathcal{Q}$, thereby ensuring our diagram (6) is licensed. At first sight, (6) looks like a typical set-up for seeking a Kan extension of F along the inclusion functor ι:

$$\begin{tikzcd} \mathcal{Q}_f \arrow[rr, "F"] \arrow[dr, hook, "\iota"'] & \arrow[d, phantom, "\Downarrow\eta"] & \mathcal{D} \\ & \mathcal{Q} \arrow[ur, dashed, "\mathrm{Lan}_\iota F"'] & \end{tikzcd} \quad \text{or} \quad \begin{tikzcd} \mathcal{Q}_f \arrow[rr, "F"] \arrow[dr, hook, "\iota"'] & \arrow[d, phantom, "\Uparrow\epsilon"] & \mathcal{D} \\ & \mathcal{Q} \arrow[ur, dashed, "\mathrm{Ran}_\iota F"'] & \end{tikzcd} \tag{7}$$

But the components of the natural transformation η or ϵ would then have to operate in the cramped quarters of $\mathcal{D}$, allowing for only the coarsest possible approximation to the desired extension.

By exchanging the roles of $\mathcal{Q}$ and $\mathcal{D}$, however, we create the opportunity for natural transformations operating in the finer granularity of $\mathcal{Q}$. Consider therefore the left Kan extension of the inclusion functor ι along F:[6]

$$\begin{tikzcd} \mathcal{Q}_f \arrow[rr, hook, "\iota"] \arrow[dr, "F"'] & \arrow[d, phantom, "\Downarrow\eta"] & \mathcal{Q} \\ & \mathcal{D} \arrow[ur, dashed, "G=\mathrm{Lan}_F\iota"'] & \end{tikzcd} \quad \begin{tikzcd} \mathcal{Q}_f \arrow[rr, hook, "\iota"] \arrow[dr, "F"'] & \arrow[d, phantom, "\Downarrow\gamma"] & \mathcal{Q} \\ & \mathcal{D} \arrow[ur, "G'"'] & \end{tikzcd} = \begin{tikzcd} \mathcal{Q}_f \arrow[rr, hook, "\iota"] \arrow[dr, "F"'] & \arrow[d, phantom, "\eta\Downarrow"] & \mathcal{Q} \\ & \mathcal{D} \arrow[ur, bend left, "G"] \arrow[ur, bend right, "G'"'] \arrow[ur, phantom, "\overset{\exists!}{\underset{\alpha}{\Rrightarrow}}"] & \end{tikzcd} \tag{8}$$

in which the so-called 'pasting diagram' on the right states a universal mapping property of $G = \mathrm{Kan}_F\iota$, that any other $\mathcal{D} \xrightarrow{G'} \mathcal{Q}$ with natural transformation $\iota \overset{\gamma}{\Longrightarrow} G'F$ must have γ factoring uniquely through η.

In this context specifically, the abovementioned natural transformations are simply finite collections of arrows '$\preceq$' of the preorder $\mathcal{Q}$, indexed either by $\mathcal{Q}_f$ or (in the case of α) by $\mathcal{D}$. The diagrams above therefore reduce to 'vectorized' statements about the images of $\mathcal{Q}_f$ under ι and GF.

$$\mathcal{Q}_f \preceq GF\mathcal{Q}_f \preceq G'F\mathcal{Q}_f. \tag{9}$$

By serially restricting (9) to the nested sequence $\mathcal{Q}_{f\downarrow d} = F^{-1}(\downarrow d) \subset \mathcal{Q}_f$ of preimages of the lower sets of $\mathcal{D}$, we obtain equivalently that

$$\mathcal{Q}_{f\downarrow d} \subseteq \downarrow G(d) \quad \forall d \in \mathcal{D}, \tag{10}$$

the $G(d)$ being by definition the *lowest* such tallies for which this holds. Now (10) in turn can be translated as

$$F(q) \le d \Longleftarrow q \preceq G(d), \tag{11}$$

which suggests the following definition.

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:*

[6]See Riehl, p.190, from which these diagrams are drawn nearly verbatim.

$$\begin{tikzcd} \mathcal{Q} \arrow[rr, "E" description] \arrow[rr, phantom, bend left=20, "\top"] & & \mathcal{D} \arrow[ll, bend right, "G"'] \end{tikzcd}$$

or

$$\begin{tikzcd} \mathcal{Q} \arrow[rr, "E" description] \arrow[rr, phantom, bend right=20, "\top"] & & \mathcal{D} \arrow[ll, bend left, "L"] \end{tikzcd}\ ,$$

(An adjunction between preorders is called a Galois connection, hence the name.)

Thus, in the case of a lower Galois enrollment $E \dashv G$, the upper adjoint G provides the rule,

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

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

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

One appeal of a Galois enrollment is that it yields a simple rule parametrized by a selection of $D + 1$ tallies, and based on the easy calculation of '$\preceq$' via matrix arithmetic as in the proof of Theorem 2.14. Writing $G(d) = g_d$, we have parameters $\{g_0, ..., g_D\} \subset \mathcal{Q}$ defining a lower-Galois enrollment by partitioning $\mathcal{Q}$ in a bottom-up cascade: $q \preceq g_0 \implies E(q) = 0$, 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 defining a right-Galois enrollment.

Now if we wish to proceed *cautiously* in approximating some given trial with final dose recommendations $\mathcal{Q}_f \xrightarrow{F} \mathcal{D}$, we must ensure $E(q) \leq F(q)\ \forall q \in \mathcal{Q}_f$. For a lower-Galois approximation, this requires

$$F(q) \leq d \implies q \preceq g_d \quad \forall q \in \mathcal{Q}_f,\ d \in \mathcal{D}, \tag{12}$$

and for an upper-Galois approximation,

$$d \not\leq F(q) \implies \ell_d \not\preceq q \quad \forall q \in \mathcal{Q}_f,\ d \in \mathcal{D}. \tag{13}$$

Closest approximations will be had with minimal such g_d's or ℓ_d's.

4.3 Lower-Galois enrollments for the 2-dose 3+3 trial

```
qs_d_nmax(Qs, D, Nmax) :- % Enumerate q ∈ Q^D with denominators up to Nmax
  length(Qs, D),
  maplist(\Q^T^N^(Q = T/N), Qs, Ts, Ns),
  Ns ins 0..Nmax, label(Ns),
  maplist(\T^N^(T in 0..N), Ts, Ns), label(Ts).

% Qfs is the subset of Q_f with recommended dose in Range
qfs_rec(Qfs, Range) :- findall(Qf, (mendtally_rec(Qf, D), D in Range), Qfs).
```

```
g_rec(G, Rec) :- % G is a valid g_Rec for the 2-dose 3+3 trial
    Rec in 0..2, indomain(Rec),
    qfs_rec(Qls, 0..Rec),
    #Rec1 #= Rec + 1,
    qfs_rec(Qhs, Rec1..2),
    qs_d_nmax(G, 2, 6),
    tfilter(\Q^(Q ≼ G), Qhs, []), % no Qh falsely identified
    tpartition(\Q^(Q ≼ G), Qls, _, []). % no Ql gets missed

?- setof(G0, g_rec(G0, 0), G0s).
%@    G0s = [[0/4,2/6],[1/5,0/4],[1/5,0/5],[1/5,0/6],[1/5,1/5],
%@           [1/5,1/6],[2/6,0/4],[2/6,0/5],[2/6,0/6]].

?- setof(G1, g_rec(G1, 1), G1s).
%@    G1s = [[0/6,2/6]].

?- setof(G2, g_rec(G2, 2), G2s).
%@    G2s = [[0/6,0/5],[0/6,0/6]].
```

Thus, for the 2-dose 3+3 trial design, we find (somewhat remarkably) that solutions (g_0, g_1, g_2) exist for the upper adjoint G even without extending our basic preorder $\preceq$. Indeed, we may have obtained as many as 18 distinct trial designs as a result, with properties worth comparing.

One reason this result is of interest is that it may provide a formal and general basis for solving the problem of 'rolling enrollment' [4] for trial designs conceived in idealized terms which do not take account of practical realities such as unsynchronized arrivals of eligible trial participants, and pending toxicity evaluations [5].

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