Applications of modules on unital quantales

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Simple applications require no more than simple formalism to explain them.

Complicated calls for complicated.

Simple for complicated simplifies and disrespects the complicated. Complicated for simple is "overmathematization", if there is a difficulty to provide reasonable interpretations of the model.

Theory acceptance in relation to and as based on dealing mostly with simple examples, runs the risk of not sufficiently well driving theory development out from shallow waters. As an example, description logic for health ontology is, as a logic, not rich enough to captures all subtleties connected with terminologies and their dependencies.

Mathematical structures in SUP have real world applications!

Objects of SUP are complete lattices. We have the task to explain the role of the elements of complete lattices and the role of the underlying partial order.

- We understand the elements of lattices as states, because these are phenomena changing after an action has been applied.
- We understand the underlying partial order as the hierarchy between levels of, on the one hand, disorder, and, on the other hand, grades of evidence in clinical guidelines as undestood within Evidence-Based Medicine (EBM).

Does many-valuedness start from two-valuedness or three-valuedness?

- In the two-valued case, Boole attaches "all beings" to 1 and "no beings" to 0, as related to geometric logic.
- In the three-valued case $\{0, a, 1\}$, how should we understand *a*?
- The fuzzy community argues that *a* is a degree of truth, more like an attitude than as a semantics.
- Bočvar calls *a* "senseless", and Kleene calls it "undefined".
- Łukasiewicz was interpreting *a* as the probability of truth, where he was changing the meaning of truth values coming from Boole and Frege.

- If truth is seen as an ontological notion, the interpretation given by the fuzzy community is meaningless in the sense of not leaning on some ontology.
- Scott's geometric logic views a as a domain of truth distinct from the total (1) and empty (0) domain of truth in the sense of Boole.
- Truth is context dependent and the size of the domain of truth is changing in a sheaf-theoretic view, sometimes being larger, sometimes smaller, and this suggests to put a in between 1 and 0.
- This gives the three chain $C_3 = \{0, a, 1\}$ which is the unique complete lattice structure on a set of three elements.

Health care involves information related to disease, functioning and condition, and related interventions

Disease and disorder is sometimes understood as the same concepts, but the medical domain provides no strict definitions.

Functioning is a counterpart to disease, a bit similar as social care is the counterpart and complement for health care.

Condition is less clear, as it combines the two, and involves also aspect than just disease and functioning.

Whereas disease and functioning are classified, conditions are harder to classify, but embrace both disease and functioning. In ageing, these mixtures become very visible.

Intervention can involve drugs, surgery, physiotherapy, i.e., interventions with shorter duration and being more instant, but also with longer duration and being more like processes and care pathway. Common to all interventions is the necessity to have a expected outcome of the intervention. Ongoing treatment can be seen as annotated with condition, aiming at favourably affecting the condition.

Prevention is yet another concept, and complicates the overall picture of classifications in health, and the view of integrated care pathways.

Information and Process must be connected!

Examples of terminologies in health care

- WHO's ICD (diseases) and ICF (functioning) as Reference Classifications
- ATC/DDD (drugs) as a Derived Classification
- IHTSDO's SNOMED as a structure of concepts equipped with description logic as its underlying logic for ontology (But note: 'Ontology' in health ontology and web ontology is not the same thing! Web ontology does not come with rigorous terminologies.)
- How to use terminology as part of providing documentation about treatment of various health conditions?

Intuitively, classifications involve typing and underlying signatures.

Who, Where, What, Why, How

- Who: Respective professionals recognized by their a) competence (education), b) job title, c) work content.
- Where: Point-of-Care, e.g., in ageing ranging from home care to ward.
- What: **Information** in form of terminology based data as expressions, and expressions in turn appearing within rules in treatment guidelines.
- Why: Objectives.
- How: Intervention as a **Process**, and intervention also as sequences and compositions of interventions crossing over professionals (Who) and points of care (Where).

In applications, for example in health care, many-valuedness modelled using quantales plays an important role. ICF's generic scale has five (5) values, and an explicit sixth value for 'not specified'. ICD is two-valued in the sense that either the diagnose is or isn't. There is implicitly a third value for 'not (yet) known' or 'suspected'. In the case of condition, and as viewed being closer to a disease related condition, we may see it more like a three-valued than a six-valued issue.

Numerics cannot compute with 'unspecified' or 'missing'. In logic and algebra we can.

We present variations of the three chain modules C_3 over unitalization of the three chain quantale C_3 is the smallest possible quantale to model many-valuedness), thus, variations of right actions are given.

Health care communities and professionals comply with a range classifications and terminologies, also including scales to qualify strength or hierarchies of evidence (in the sense of *evidence-based medicine*) or interaction, or as related to levels of functioning. Such hierarchies adopted in health care are ad hoc as compared to the potentially algebraic and logic structures of terminology infused reasoning. We show how these hierarchies canonically derive as actions where transitions appear as levels in hierarchies of evidence.

We will also see how three-valuedness related to health conditions, rather than two-valuedness, is the generator of many-valuedness related to strength of evidence.

Bivalence is fundamental in health and related statistical computation. Sampling often involves hesitation about a patient being suitable in a population related to a randomized clinical trial (RCT). In cohorts, inclusion is based on some criteria, and debate often appears about criteria perhaps not being sharply and unambiguously defined.

Mean values cannot be computed until we ’believe sharply’ in the numbers it involves. By the time mean values are computed, many-valuedness as related to subject inclusion in the process of sampling is hidden and thereafter ignored as statistics continue to apply its machinery and produce ’evidence’ as appearing in Evidence-Based Medicine (EBM).

Uncertainty obviously re-enters, but in a different form and in connection with variances attached to mean values. Trials and studies are about explaining outcomes of action in form of intervention or prevention, where interventions can involve drug treatment, surgery, or other types of actions expected to intervene with disease and its possible progression.

Bivalence appears then in the way outcomes are classified as successful or unsuccessful. This bivalent classification then divides a population into two parts, one side said to fulfill a given hypothesis, the other side not fulfilling. Strength of evidence is then connected with the values quantifying the acceptance or rejection of such a hypothesis. Acceptance and rejection are not logically antithetic, so ’evidence’ in the sense of EBM is not to be confused with ’truth’ in the sense of logic.

In the plethora of studies, there is a need for comparison, and a requirement to arrive at common judgment. Studies involving the same medical problem or treatment hypothesis, when compared, may appear inconsistent with respect to populations and inclusion criteria involved. Systematic reviews produced by the medical communities then involve such plethora of studies for which consensus statements are required.

However, rules appearing in such consensus guidelines are even further away from becoming subjected to logical investigations, since underlying signatures and terms, i.e., from logical point of view, are tremendously difficult to identify. Terminology and classification helps, but studies are unfortunately reluctant to comply with formal involvement of encodings to control sampling in production of populations appearing in RCTs.

Bivalence in health is thus rooted in, and kind of imprisoned by, the statistical machinery adopted in EBM. Many-valuedness then appears, as we already said, e.g., in connection with uncertainty arising in hypothesis testing, but it arises in an ad hoc way also in *grading of evidence*, which has become a standard for representing levels of evidence in systematic reviews and meta-analyses.

Such grades, and in various modified forms, appear also, e.g., in drug interactions. A similar grade, even if not in form of grades of evidence, but as related to quantifying populations, appears in a generic scale for providing scales related to functioning and disability.

We intend to show how **grading of evidence canonically can be derived from a three-valued, not two-valued, chain describing the qualification of a health condition**.

An intervention is caused by a multiple disease and multiple functioning related 'state of condition', where **the goal of an intervention is to stabilize or improve the condition, in order to stop its progression into an even worse situation becoming chronic**.

This calls for the three-valuedness as related to health conditions, including the states

- condition under control or problem removed ($\top$),
- condition that requires intervention (a),
- condition not improvable by intervention ($\bot$).

Interventions having desirable and ideal effect would change a condition state from a to $\top$. Interventions basically having no effect would leave condition states unchanged. The relation between $\top$, a and $\bot$ represents a hierarchy expressed by the partial order on C_3.

An interesting (and necessary) bivalence relates to the intervene or not question.

We either intervene or we don't, and this bivalence appears as the two-valued unital quantale which appears in the steps where we provide the unitalization $\widehat{C_3}$ of $C_3 = \{\bot, a, \top\}$,

where the unitalization will be shown to embrace the hierarchy of transitions corresponding to success levels of interventions, i.e., implicitly corresponding to levels of evidence.

In this paper we suggest that interventions can be identified as (condition state) transitions in an action $C_3 \otimes \mathfrak{Q} \xrightarrow{\boxdot} C_3$. In that right action, we adopt $(\mathfrak{Q}, *, e)$ to be a unital quantale as a monoid in $\mathtt{Sup}$, the monoidal closed category of complete lattices with join preserving maps. As will be shown, the structure of $\mathfrak{Q}$, together with its action on C_3, will embrace the health professions understanding of condition states and evidence levels, and even how they are algebraically related.

Levels of evidence are in fact canonically derived from levels of condition states.

Let $C_3^r = (C_3, *_r)$ be the non-commutative, idempotent, right-sided chain of three elements $\{\bot, a, \top\}$ and $C_3^l = (C_3, *_\ell)$ be the non-commutative, idempotent, left-sided chain of the same $\{\bot, a, \top\}$, i.e., with C_3 in our application corresponding to a set of conditions. For the right-sided C_3 we have

$$a *_r \top = a, \quad \top *_r a = \top, \quad a *_r a = a,$$

and for left-sided we have

$$\top *_\ell a = a, \quad a *_\ell \top = \top, \quad a *_\ell a = a.$$

From application point of view,

the interpretation of $a *_r \top$ is that **condition** *a* **overwrites the satisfactory condition** $\top$,

so that the decision about starting or not starting a treatment is taken based on diseases and functioning underlying and related to condition state *a* on the left-hand side of the expression $a *_r \top$.

A concrete situation occurs e.g. in hypertension treatment with hypertension as a disease and dizziness (functioning) as a side-effect of a selected drug treatment. Hypertension is given higher priority than dizziness, so hypertension is left-sided in the expression. Hypertension in state a could mean that treatment goals (blood pressure limits) have not yet been reached, and dizziness at $\top$ could mean that it is mild only and not restricting daily functioning.

Treatment therefore continues from the viewpoint of $a *_r \top = a$ with the goal to reach blood pressure limits.

Thus, $*_r$ enables conditions to overwrite one another (from left to right), so that $*_r$ prevails the first argument, whereas $*_\ell$ prevails the second argument.

A right $\mathfrak{Q}$-module $(C_3, \boxdot)$ is the complete lattice C_3 with a right action $C_3 \otimes \mathfrak{Q} \xrightarrow{\boxdot} C_3$ over $(\mathfrak{Q}, *, e)$. Further, let $[C_3, C_3]$ be the complete lattice of all join preserving self-maps of C_3 and $([C_3, C_3], \circ, 1_{C_3})$ is the corresponding unital quantale. It is well known that every right action $\boxdot$ on C_3 can be identified with a unital quantale homomorphism $\mathfrak{Q}^\tau \xrightarrow{h} [C_3, C_3]$ such that the relation $x \boxdot \alpha = h(\alpha)(x)$ holds for all $x \in C_3$ and $\alpha \in \mathfrak{Q}$.

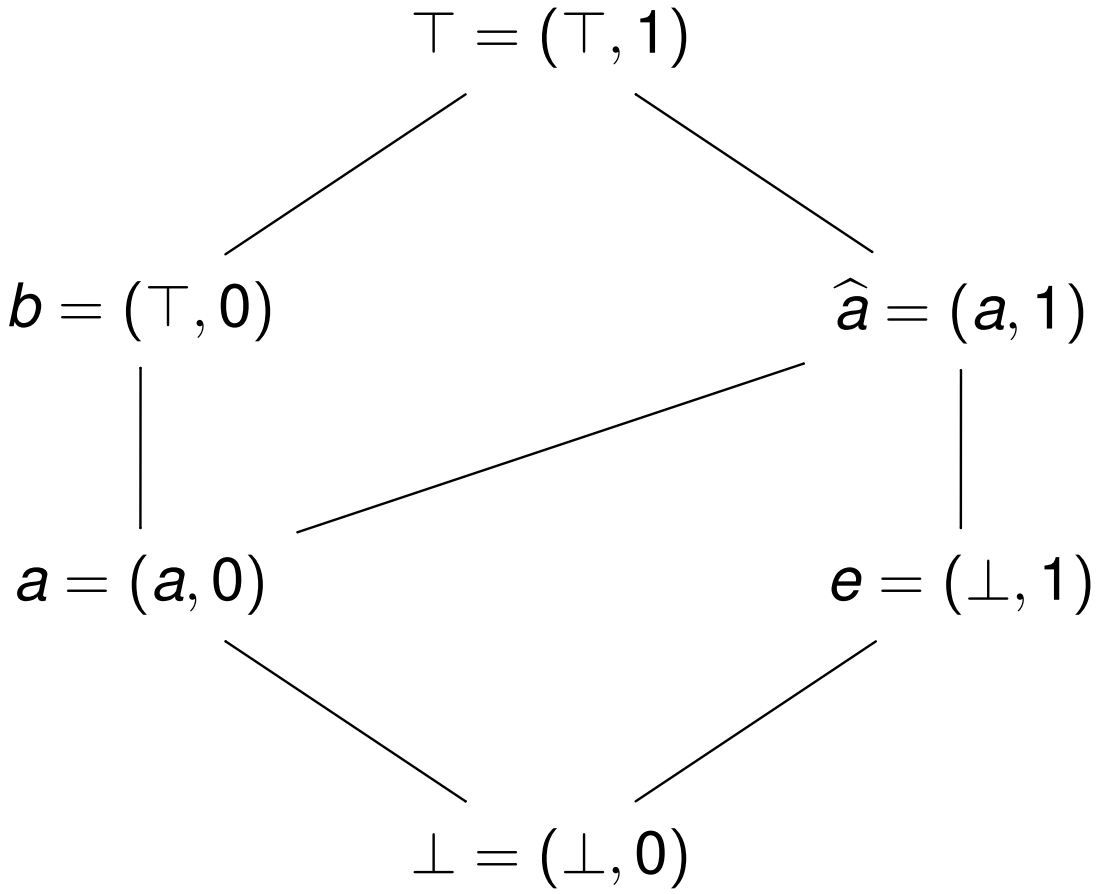
Note how such an $h(\alpha)$ in the applications represents a state transition, either expected or as actually happened. Since α, as we shall see, corresponds to an evidence level, the application oriented reading of $h(\alpha)(x)$ is the expected condition to be the outcome of an intervention related to condition x, given evidence level α for the selected intervention.

Further, let $\widehat{C_3^r}$ be the unitalization of C_3^r and $\widehat{C_3^l}$ be the unitalization of C_3^l. Hence the underlying set is given by $\{\bot, a, \top\} \times \{0, 1\}$ whose elements we abbreviate as follows: $(\bot, 0) = \bot, (a, 0) = a, (\top, 0) = b, (\bot, 1) = e, (a, 1) = \widehat{a}, (\top, 1) = \top$.

Note how $\{0, 1\}$ now enlarges the set C_3 of conditions to the underlying set of the unitalization, which is expected in the end to embrace levels of evidence.

The application oriented interpretation of $\{0, 1\}$ therefore is related to the binary decision of treating or not treating.

Then we have the following Hasse diagram and multiplication table:



$\widehat{*_r}$	$\bot$	a	b	e	$\widehat{a}$	$\top$
$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$
a	$\bot$	a	a	a	a	a
b	$\bot$	b	b	b	b	b
e	$\bot$	a	b	e	$\widehat{a}$	$\top$
$\widehat{a}$	$\bot$	a	b	$\widehat{a}$	$\widehat{a}$	$\top$
$\top$	$\bot$	b	b	$\top$	$\top$	$\top$

$\widehat{*_\ell}$	$\bot$	a	b	e	$\widehat{a}$	$\top$
$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$
a	$\bot$	a	b	a	a	b
b	$\bot$	a	b	b	b	b
e	$\bot$	a	b	e	$\widehat{a}$	$\top$
$\widehat{a}$	$\bot$	a	b	$\widehat{a}$	$\widehat{a}$	$\top$
$\top$	$\bot$	a	b	$\top$	$\top$	$\top$

Note that the transposed multiplication of $*_r$ is precisely $*_\ell$. It is also easy to check that for each prequantale $(X, *)$, the unitalization of the transposed prequantale and the transposed of the unitalization coincide, i.e., $(\widehat{X}, \widehat{*^\tau}) = (\widehat{X}, \widehat{*}^\tau)$.

In particular we have that $\widehat{C_3^\ell} = (\widehat{C_3}, \widehat{*_\ell}) = (\widehat{C_3}, \widehat{*_r}^\tau) = \widehat{C_3^r}^\tau$.

$$(x,0)\,\widehat{*^\tau}\,(y,0) = (x *^\tau y, 0) = (y * x, 0) = (y,0)\,\widehat{*}\,(x,0),$$

$$(x,1)\,\widehat{*^\tau}\,(y,1) = ((x *^\tau y) \vee x \vee y, 1) = ((y * x) \vee x \vee y, 1)$$

$$= (y,1)\,\widehat{*}\,(x,1),$$

$$(x,1)\,\widehat{*^\tau}\,(y,0) = ((x *^\tau y) \vee y, 0) = ((y * x) \vee y, 0) = (y,0)\,\widehat{*}\,(x,1)$$

$$(y,0)\,\widehat{*^\tau}\,(x,1) = ((y *^\tau x) \vee y, 0) = ((x * y) \vee y, 0) = (x,1)\,\widehat{*}\,(y,0).$$

In the application view, operators $\widehat{*}$ in the application view now *aggregate* levels of evidence in situations where two separate interventions (related to separate clinical guidelines), are applied, with respective levels of evidence.

In this case, one of the interventions is the prime intervention, even if interventions are applied simultaneously.

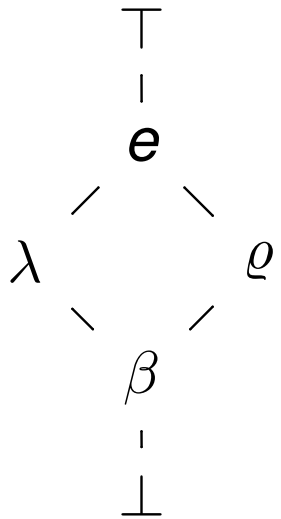
For instance, $(\perp, 0) \mathbin{\widehat{*_r}} u = (\perp, 0)$ would mean that a non-preferred treatment for a condition at $\perp$ in combination and having expected joint effect with any other treatment, preferred or not, for another condition, remains at a level of evidence at $(\perp, 0)$, i.e., remains as non-preferred 0 for the joint condition $\perp$.

Note how (x, τ), where x is the condition and τ the decision or recommendation to treat or intervene hides, on the one hand, information and codes about the particular diseases and functioning together establishing the health condition called x, and, on the other hand, specific description and codes about the intervention noted as (x, τ). In the case of a drug intervention, (x, τ) would hide the specific drug code.

Further, let $[C_3, C_3]$ be the unital quantale of all join preserving self maps of $C_3 = \{\bot, a, \top\}$. Then we have $[C_3, C_3] = \{\bot, \beta, \lambda, \varrho, e, \top\}$ where

$$\beta(a) = \bot,\ \beta(\top) = a,\ \lambda(a) = \bot,\ \lambda(\top) = \top,\ \varrho(a) = a,$$
$$\varrho(\top) = a, e = \mathrm{id}_{C_3},\ \top(a) = \top,\ \top(\top) = \top.$$

Then the Hasse diagram and its related multiplication table are given by



$\circ$	$\bot$	β	λ	ϱ	$\boldsymbol{e}$	$\top$
$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$	$\bot$
β	$\bot$	$\bot$	β	$\bot$	β	ϱ
λ	$\bot$	$\bot$	λ	$\bot$	λ	$\top$
ϱ	$\bot$	β	β	ϱ	ϱ	ϱ
$\boldsymbol{e}$	$\bot$	β	λ	ϱ	$\boldsymbol{e}$	$\top$
$\top$	$\bot$	λ	λ	$\top$	$\top$	$\top$

Note now the distinction in interpretations, respectively, of $\widehat{C}_3^r$ and $[C_3, C_3]$ whereas C_3 represents levels of conditions, $\widehat{C}_3^r$ conjuncts levels of conditions with binary treatment decisions. As such, $\widehat{C}_3^r$ does not enable valuation of strength of evidence of an underlying treatment guideline, but $\widehat{C}_3^r$ supports trials leading to estimating the strength of evidence. This shift from evidence creation to actual levels of evidence, as represented by $[C_3, C_3]$, is described by the homomorphisms between $\widehat{C}_3^r$ and $[C_3, C_3]$.

Seemingly, the operation $\widehat{*_r}$ is non-commutative so suggested interventions appear in a given order or priority. Note that composition of maps is purely sequential. This also, in its right, explains the difference between co-morbidity and multi-morbidity.

Observation. $\widehat{C_3^r}$ does not have nontrivial zero divisors, but in $[C_3, C_3]$ we have β and λ left non-zero divisors and β and ϱ as right non-zero divisors, because
$\beta \circ \beta = \lambda \circ \beta = \beta \circ \varrho = \lambda \circ \varrho = \bot$.

There exist 6 different unital homomorphisms $\widehat{C_3^{\ell}} \xrightarrow{h_i} [C_3, C_3]$ $(i = 1, 2, 3, 4, 5, 6)$ —namely:

$h_1(\bot) = \bot$, $h_1(e) = e$, $h_1(a) = h(b = h_1(\widehat{a}) = h_1(\top) = \top$,
$h_2(\bot) = \bot$, $h_2(a) = h_2(b) = h(\widehat{a}) = h_2(\top) = h_2(e) = e$,
$h_3(\bot) = \bot$, $h_3(a) = \lambda$, $h_3(b) = h_3(\top) = \top$, $h_3(e) = h_3(\widehat{a}) = e$,
$h_4(\bot) = \bot$, $h_4(a) = h_4(b) = \lambda$, $h_4(\top) = h_4(e) = h_4(\widehat{a}) = e$.
$h_5(\bot) = \bot$, $h_5(a) = h_5(b) = \varrho$, $h_5(\top) = h_5(e = h_5(\widehat{a}) = e$.
$h_6(\bot) = h_6(a) = h_6(b) = \bot$, $h_6(\top) = h_6(e) = h_6(\widehat{a}) = e$.

There are 6 different right actions $\boxdot_i$ on $X = C_3 = \{\bot, a, \top\}$ with respect to the unital quantale $\mathfrak{Q} = \widehat{C_3^r}$. Namely,

$$\begin{array}{llll}
\top \boxdot_1 a = \top, & \top \boxdot_1 b = \top, & \top \boxdot_1 \top = \top, & \top \boxdot_1 e = \top, \\
\top \boxdot_1 \widehat{a} = \top, & a \boxdot_1 a = \top, & a \boxdot_1 b = \top, & a \boxdot_1 \top = \top, \\
a \boxdot_1 e = a, & a \boxdot_1 \widehat{a} = \top, & &
\end{array}$$

$$\begin{array}{llll}
\top \boxdot_2 a = \top, & \top \boxdot_2 b = \top, & \top \boxdot_2 \top = \top, & \top \boxdot_2 e = \top, \\
\top \boxdot_2 \widehat{a} = \top, & a \boxdot_2 a = a, & a \boxdot_2 b = a, & a \boxdot_2 \top = a, \\
a \boxdot_2 e = a, & a \boxdot_2 \widehat{a} = a, & &
\end{array}$$

$$\begin{array}{llll}
\top \boxdot_3 a = \top, & \top \boxdot_3 b = \top, & \top \boxdot_3 \top = \top, & \top \boxdot_3 e = \top, \\
\top \boxdot_3 \widehat{a} = \top, & a \boxdot_3 a = \bot, & a \boxdot_3 b = \top, & a \boxdot_3 \top = \top, \\
a \boxdot_3 e = a, & a \boxdot_3 \widehat{a} = a, & &
\end{array}$$

$$\begin{array}{llll}
\top \boxdot_4 a = \top, & \top \boxdot_4 b = \top, & \top \boxdot_4 \top = \top, & \top \boxdot_4 e = \top, \\
\top \boxdot_4 \widehat{a} = \top, & a \boxdot_4 a = \bot, & a \boxdot_4 b = \bot, & a \boxdot_4 \top = a, \\
a \boxdot_4 e = a, & a \boxdot_4 \widehat{a} = a, & &
\end{array}$$

$$\begin{array}{llll}
\top \boxdot_5 a = a, & \top \boxdot_5 b = a, & \top \boxdot_5 \top = \top, & \top \boxdot_5 e = \top, \\
\top \boxdot_5 \widehat{a} = \top, & a \boxdot_5 a = a, & a \boxdot_5 b = a, & a \boxdot_5 \top = a, \\
a \boxdot_5 e = a, & a \boxdot_5 \widehat{a} = a, & &
\end{array}$$

$$\begin{array}{llll}
\top \boxdot_6 a = \bot, & \top \boxdot_6 b = \bot, & \top \boxdot_6 \top = \top, & \top \boxdot_6 e = \top, \\
\top \boxdot_6 \widehat{a} = \top, & a \boxdot_6 a = \bot, & a \boxdot_6 b = \bot, & a \boxdot_6 \top = a, \\
a \boxdot_6 e = a, & a \boxdot_6 \widehat{a} = a. & &
\end{array}$$

with the following antisymmetric $\widehat{C_3^r}$-preorders:

$p_1(a,a) = e, \quad p_1(\top,\top) = \top, \quad p_1(\top,a) = \bot,$
$p_1(a,\top) = \top, \quad p_1(\bot,\bot) = \top, \quad p_1(\top,\bot) = p_1(a,\bot) = \bot,$
$p_1(\bot,a) = p_1(\bot,\top) = \top,$

$p_2(a,a) = \top, \quad p_2(\top,\top) = \top, \quad p_2(\top,a) = \bot,$
$p_2(a,\top) = \top, \quad p_2(\bot,\bot) = \top, \quad p_2(\top,\bot) = p_2(a,\bot) = \bot,$
$p_2(\bot,a) = p_2(\bot,\top) = \top,$

$p_3(a,a) = \widehat{a}, \quad p_3(\top,\top) = \top, \quad p_3(\top,a) = \bot,$
$p_3(a,\top) = \top, \quad p_3(\bot,\bot) = \top, \quad p_3(\top,\bot) = p_3(a,\bot) = \bot,$
$p_3(\bot,a) = p_3(\bot,\top) = \top,$

$p_4(a,a) = \top, \quad p_4(\top,\top) = \top, \quad p_4(\top,a) = \bot,$
$p_4(a,\top) = \top, \quad p_4(\bot,\bot) = \top, \quad p_4(\top,\bot) = p_4(a,\bot) = \bot,$
$p_4(\bot,a) = p_4(\bot,\top) = \top,$

$p_5(a,a) = \top, \quad p_5(\top,\top) = \top, \quad p_5(\top,a) = b,$
$p_5(a,\top) = \top, \quad p_5(\bot,\bot) = \top, \quad p_5(\top,\bot) = \bot,$
$p_5(a,\bot) = \bot, \quad p_5(\bot,a) = p_5(\bot,\top) = \top,$

$p_6(a,a) = \top, \quad p_6(\top,\top) = \top, \quad p_6(\top,a) = b,$
$p_6(a,\top) = \top, \quad p_6(\bot,\bot) = \top, \quad p_6(\top,\bot) = b,$
$p_6(a,\bot) = b, \quad p_6(\bot,a) = p_6(\bot,\top) = \top.$

Classifications are typically tree structured, and involve levels of detail and thereby represents a granularity of information. We illuminate this below by briefly explaining the structure of classification of drugs. The Anatomic Therapeutic Chemical ATC/DDD (Anatomical Therapeutic Chemical / Defined Daily Dose) classification system is one of the Related Classifications in the WHO (World Health Organization) Family of International Classifications[1] (FIC). The drugs are classified using ATC codes appearing in five levels.

Table on next slide presents an example using nitrazepam (code N05CD02) as a drug, typically used for short term sleeping problems (insomnia).

[1] WHO website for classifications
http://www.who.int/classifications/en/

N	nervous system	1st level main anatomical group
N05	psycholeptics	2nd level, therapeutic subgroup
N05C	hypnotics and sedatives	3rd level, pharmacological subgroup
N05CD	benzodiazepine derivatives	4th level, chemical subgroup
N05CD02	nitrazepam	5th level chemical substance

ATC encodes drugs and drug interventions, where interventions in general stem from diseases and also targets functioning. From WHO classification point of view, diseases are encoded in ICD (International Classification Diseases), and functioning is encoded in ICF (International Classification of Functioning, Disability and Health). As an example, the ICD code for insomnia is G47.0, where insomnia is a sleep disorder (ICD code G47). Nitrazepam (ATC code N05CD02) is therapeutically *indicated* for the short-term treatment of insomnia (ICD code G47.0).

An example *contraindication* is acute pulmonary insufficiency (ICD code J95.2). Common side-effects of the use of nitrazepam are dizziness and unsteadiness. Note how 'dizziness' is basically undefined and uncoded when appearing in the context of listed side-effects for nitrazepam. However, 'dizziness' is formally encoded as a functioning aspect under ICF. The ICF code for Dizziness is b2401, and characterized as *Sensation of motion involving either oneself or one's environment; sensation of rotating, swaying or tilting*. Dizziness falls under ICF code b240 'Sensations associated with hearing and vestibular function', in turn part of 'Sensations of dizziness, falling, tinnitus and vertigo. Hearing and vestibular functions' (ICF codes b230-b249).

This example clearly shows the need to relate diseases, functioning and (drug) treatments, and how one domain may act on another. Interventions applied simultaneously or in sequence may interact, so that the overall effect of the intervention as whole may be lower than expected given respective interventions. This situation is clearly seen in the case of drug treatment and related drug-drug interactions. Formally speaking, drug-drug interactions are bivalent or multivalent relations. In fact, pharmacological societies do not share a common view on this valuedness issue. However, there are shared models, where the SFINX[2] drug interaction database is one of them. The information in SFINX divided into five different parts describing each pair of drugs involving an interaction: medical consequence, recommendation, mechanism, background and references.

[2] SFINX is in use in almost all pharmacies in Finland.

In SFINX, classifications A, B, C and D are defined, respectively, as 'Minor interaction of no clinical relevance.', 'Clinical outcome of the interaction is uncertain and/or may vary.', 'Clinically relevant interaction that can be handled e.g. by dose adjustments.' and 'Clinically relevant interaction. The combination is best avoided.', respectively. The classifications A and B are obviously related since they mean no or uncertain clinical relevance, whereas C and D represent clinically relevant interactions. In other words, A and B are closer to allow prescription, whereas C and D basically means not to prescribe. Further, A is stronger in favour of prescription (despite interaction) than B since A is no evidence and B is uncertain clinical outcome. Similarly, D stronger against prescription that C since D is generally best avoided, whereas C opens up a possibility to manage a clinically relevant interaction with dose adjustment.

With $L = \{A, B, C, D\} = \{\top, e, \lambda, \bot\} = \mathrm{Im}(h_3)$ as the lattice for interaction levels in *ATC*, SFINX is basically a mapping $\sigma_{SFINX} : ATC \times ATC \to L$. Whereas A-D classifies clinical relevance, the SFINX interaction model additionally include levels of documentation (0-4), which represent strength of 'evidence' in the sense of evidence-based medicine (EBM) given with statistical models only. Note that these levels combine with classifications A-D, so that whenever the classification is provided it is expected to be annotated with a corresponding level of documentation.

Note that $\{A, B, C, D\}$ similarly appears as grading of evidence[3] more generally in Evidence-Based Medicine.

[3] H. J. Schünemann, et al, *An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations*, American Journal of Respiratory and Critical Care Medicine **174** (2006), 605-614.

In our interpretation, we now have a following situation. If two conditions x and y are treated with respective drugs d_x and d_y, as interventions notated, respectively, as $(x, 1)$ and $(y, 1)$, then we expect

$$\sigma_{SFINX}(d_x, d_y) \geq h_3((x, 1) \mathbin{\widehat{*_\ell}} (y, 1)) = h_3((x, 1)) \circ h_3((y, 1))$$

i.e., the drug interaction must be proportionally less as compared to the aggregated evidence of respective drugs interventions. Or the other way around, a strong interaction between d_x and d_y will jeopardize the advantage of the aggregation of the simultaneous intervention for conditions x and y. The equality establishes a connection between order in interventions and sequentializing evidence-based treatment guidelines.

For one and the same patient with two conditions, and with treatments decided as related to respective conditions

$$(x, 1), (y, 1)$$

they represent (but hide!) specific disease and functioning **Information** (and other information, like lab results, etc.) related with the conditions x and y, and about the treatment decision 1 (more specific information about treatment also hidden!) of the condition.

Then

$$(x, 1) \mathbin{\widehat{*_\ell}} (y, 1)$$

implicitly embraces an aggregation of conditions x and y, and additionally enforces to prioritize or sequentialize one treatment over the other, where $\widehat{*_\ell}$ prescribes the order. Note that reading becomes right to left, so that $(y, 1)$ is the first priority.

The morphism h_3 provides the transition from condition with decision about treatment to an evidence level attached with the treatment. Note that we assume that decision to treat is followed by actual treatment, and as complying with the corresponding clinical guideline, with treatment detail annotated with evidence levels[4].

Then

$$h_3((x, 1)), h_3((y, 1))$$

represent evidence levels as appearing in respective guidelines.

[4] See examples of how evidence levels A, B, C and D appear in some typical clinical guidelines (e.g. Duodecim's (Finland) guideline for hypertension treatment and SIGN's (Scotland) guideline for melanoma care).

Thus

$$h_3((x,1)) \circ h_3((y,1))$$

implicitly embraces an aggregation of evidence levels.

Note how $\top \circ e = e \circ \top = \top$, i.e., the evidence for the "sequentialized treatment" of two treatments is always $\top$ if one treatment is at level $\top$ and the other not lower than e. Similarly the appearance of $\bot$ and λ level treatments together, make the sequence to $\bot$. This shows that in the subsets $\{A, B\}$ and $\{C, D\}$, evidence levels provide no order of treatment even if conditions as perceived by the patient may be ordered. Note also how a sequence involving a $\bot$ classified treatment always becomes $\bot$. In other cases and subsets, order is meaningful.

The EBM communities do not recognize this way of combining evidence, since it is not embraced by the statistical machinery. However, e.g. in the of $\{A, B\}$ and $\{C, D\}$, it does seem reasonable, and in fact brings treatment decisions in these sequentialized case back to binary treatment decisions, and thus away from evidence level qualified decisions.

Similarly we can now imagine many-valued relation in connection with $ICD \times ATC$ for drug interventions related to disease, or with $ATC \times ICF$ for functioning related side-effects of drugs, or *ICD*, *ICF* and *ATC* appearing in other products and combinations.

Indeed, in interpretations above, we simplify the situations since coding information becomes completely hidden. However, codes can be recovered. A typical situation in drug treatment is when a patient is presently using a set of drugs $\{a_1, \ldots, a_n\}$, given a set of diseases $\{d_1, \ldots, d_m\}$, an existing disease requires a drug prescription extension, or another disease d_{m+1} requires a new drug prescription. A main recommendation for drug treatment of d_{m+1} may be contraindicating with respect to diseases in $\{d_1, \ldots, d_m\}$ or be interacting with one or several drugs in $\{a_1, \ldots, a_n\}$.

Additionally, the existing set of side-effects must be considered, so that the side-effect burden is possibly not increased. Side-effect are typically found to become encoded in ICF, and ICF comes with its generic scale of five items with an additional item for 'not yet specified'. Similarly, ICD can be seen as coming with a scale with two items (a diagnosis either confirmed or not), with an additional 'not yet known' for a suspected diagnosis. This shows how the relation and actions between ICD, ICF and ATC can be quite complicated when drug treatments are given for particular diseases within a setting of multiple diseases, and one main concern is not to increase ICF burden as related to side-effects.

The relation between an intervention and a condition is important, and as we have seen, simultaneous but ordered interventions must comply with the sequence of treatment guidelines corresponding to that order. Clearly, we want quality of interventions to correlate with guidelines, so that we avoid the situation "the operation was successful (according to guideline), the patient died (given the treatment)", where the selected intervention was provably right, and the resulting condition was obviously wrong.

The question is then also how combination and aggregation of interventions should relate to the corresponding combination and aggregation of conditions. When we explicitly involve order, we realize it is even more complicated. Order comes into play also as the timely order between interventions and conditions as intertwined sequences of actions, where treatment is modified and proceeds, and conditions change also possibly due to progression of disease and possible appearance of new diseases and conditions. Looking at the whole situation over a longer period of time may and should show a good correlation between sequence of treatments and sequence of conditions, and how treatments have acted upon conditions, even if some selected subsequences may not support some view of optimality in those respects. This then comes to the question about how to formulate "goal of treatment", or "outcome" as the medical community prefers to call it. This is then where logic starts to knock on the door.

The medical community is well aware of this dilemma, but the statistical machinery is hopelessly incapable of modelling it. The medical community is still annoyed by the "plethora of studies" that basically are incomparable. Why do we often not get the right drug treatment at start, even in the case of simple treatment situations? Obviously, because that plethora of studies cannot tell us precisely how, i.e., precision medicine is still not well developed, and personalized health is still not well modelled, in particular within the realm of integrated care pathways.