Continuous-time multi-state models for cost-effectiveness analysis in health economics

Chris Jackson
MRC Biostatistics Unit
University of Cambridge, U.K.

R in CEA Workshop, UCL, July 2018

"Modelling": two cultures

Statistical modelling

- Start with a dataset
- Fit models to the data

Expertise:

- learning from data, expressing uncertainty / variation quantitatively

Health economic modelling

- Start with model of the disease/intervention
- "Populate" it with data

Expertise:

- economic, clinical, epidemiological

obtain relevant data, answer relevant question
represent quantitative evidence faithfully
inform decision making

R facilitates better statistical models

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Survival analysis and beyond, in a health economic context

Survival analysis

- Individual data on times to events / censoring
- Kaplan-Meier, Cox regression, parametric modelling ...

$\rightarrow$ expected survival over horizon

Decision-analytic modelling

- State transition modelling, discrete-time transition probabilities
- Multiple sources of data...

$\rightarrow$ expected QALYs and costs over a horizon

- What if individual-level data on more than one kind of event: e.g. times of disease progression events?
- Can model these data with a continuous-time, multi-state model

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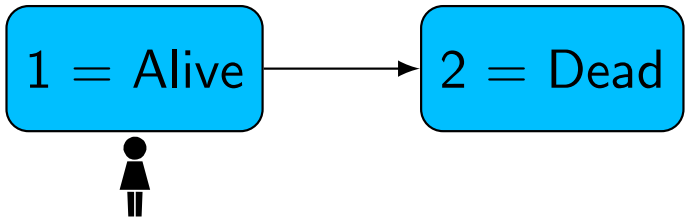
Examples of multi-state processes

Survival model



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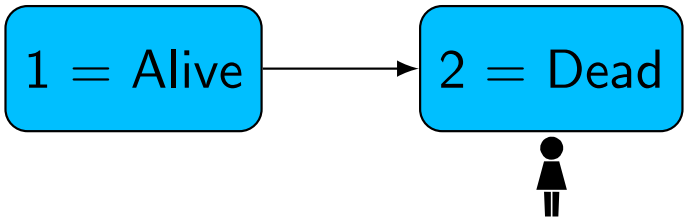

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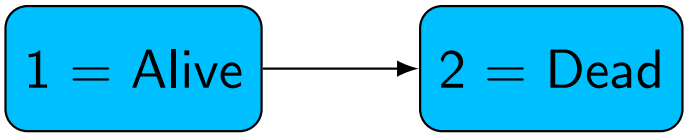
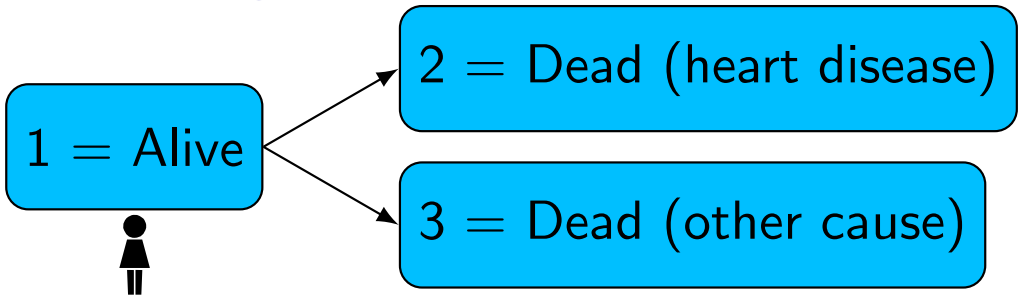


Competing risks model



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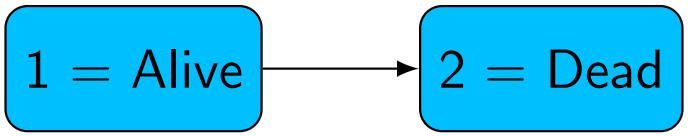

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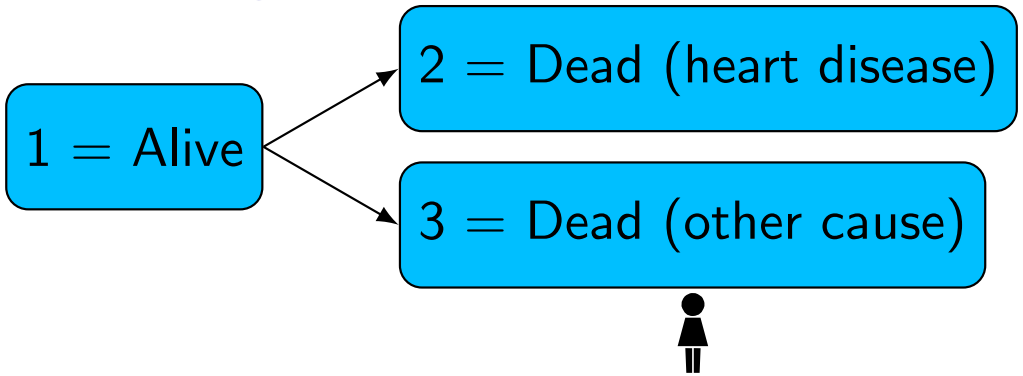

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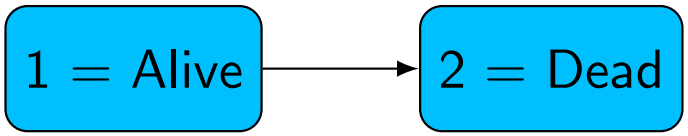

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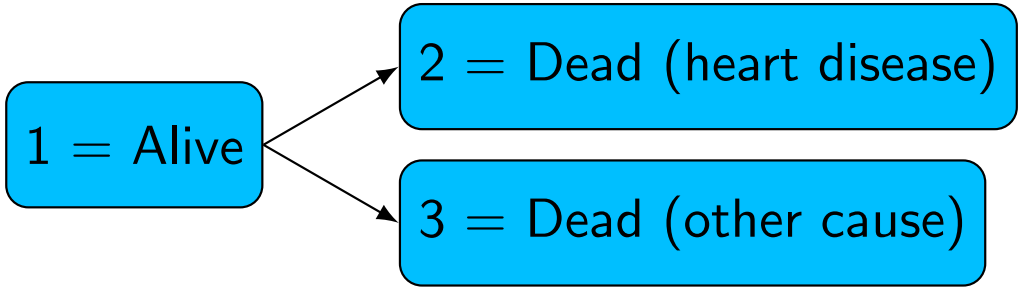
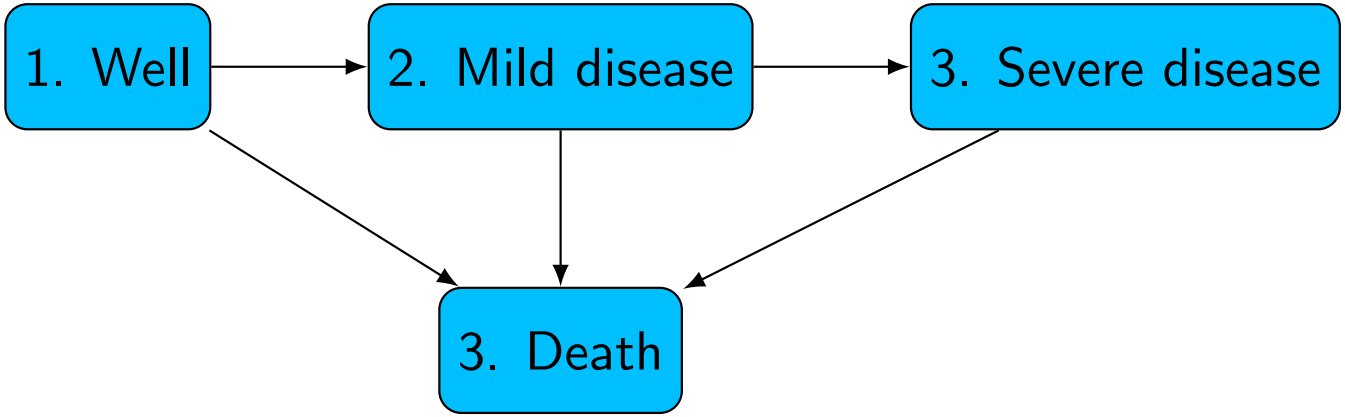


Staged disease progression model



Any state structure feasible with current tools

Transition rates for a continuous time multi-state model

Want to estimate the rates of transition between each pair of states

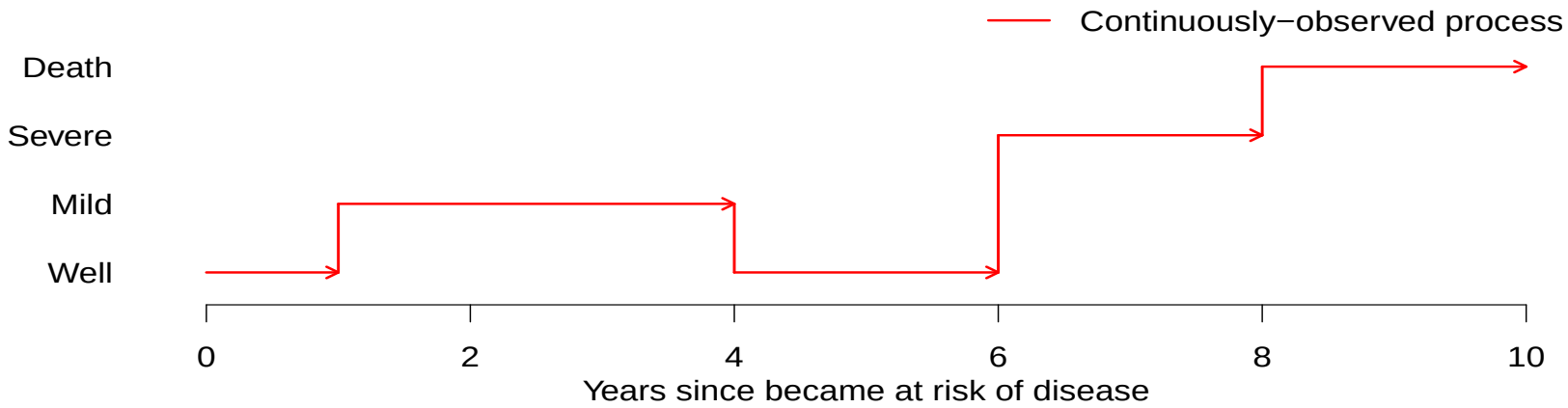
- Expected number of events given some time at risk
- Rates are not probabilities. Can be > 1
- Equivalent of hazard in survival analysis — instantaneous risk that the transition will happen

Continuous-time analogue of transition probabilities

- Prob (in state s at time $t + 1$) given state r at time t
- Given rates, can compute probabilities of transition over any discrete time interval or cycle

Alternative forms of data for multi-state modelling

Continuous observation: know state at all times



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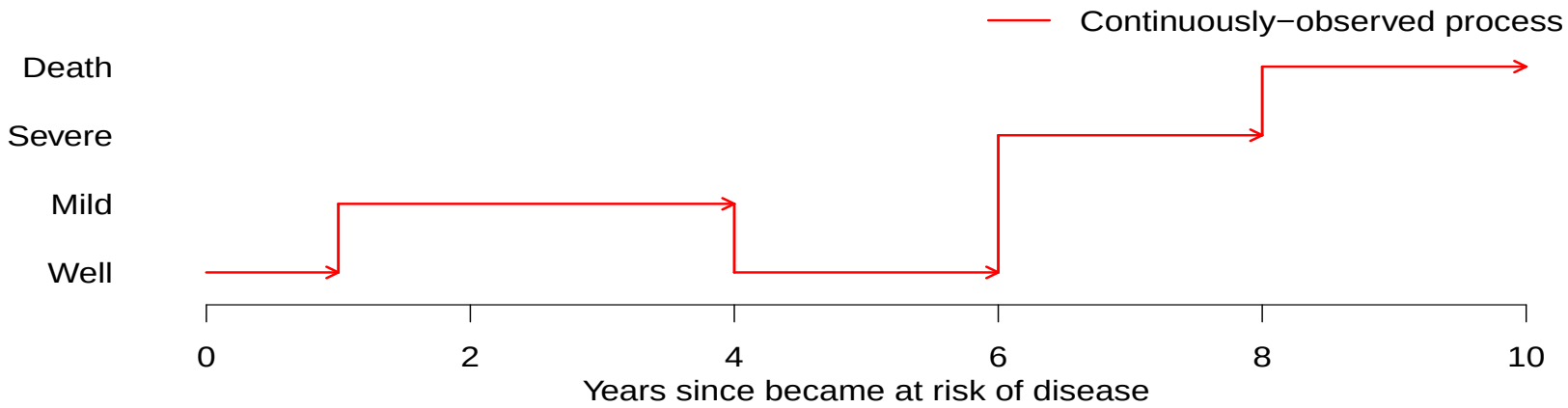
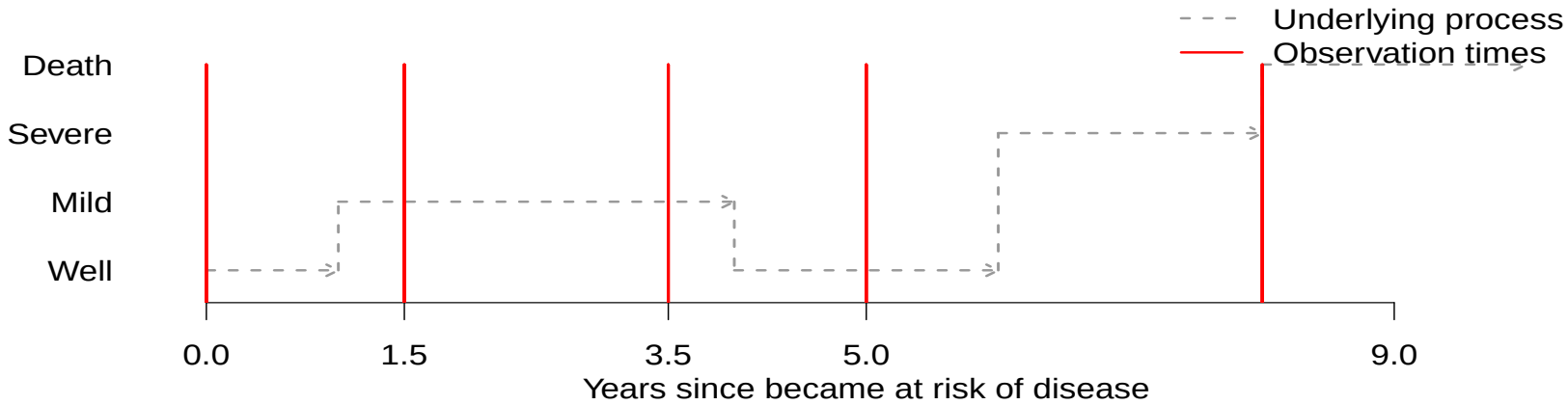


Panel data: know state at finite number of observations, transition times unknown

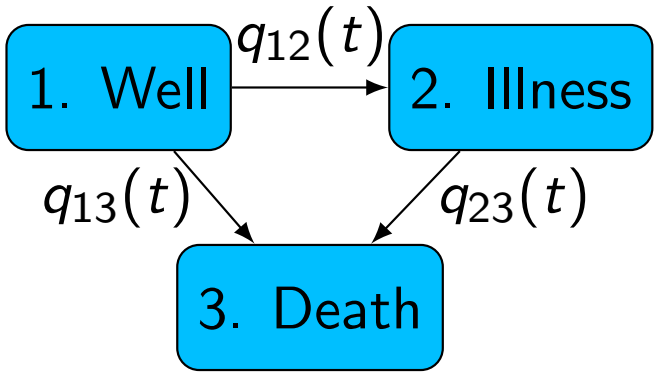


May be variants of either, e.g. death times commonly known

Continuously-observed data for multi-state modelling

Event times

Person	Time	Event	State
1	0	Start of process	1
1	45	Alive without illness	1
2	0	Start of process	1
2	65	Illness onset	2
2	85	Death	3
3	0	Start of process	1
3	25	Death without illness	3



- Estimate hazard function $q()$ for each of three transitions
- Can simply implement three time-to-event models
- Rearrange data to time-to-event format...

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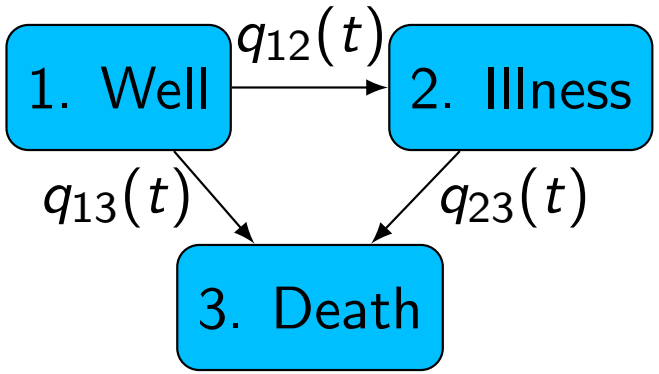

Data arranged with one row per potential transition...

Person	Start time	Stop time	Transition	Status
1	0	45	1–2	Censored
1	0	45	1–3	Censored
2	0	65	1–2	Observed
2	0	65	1–3	Censored
2	65	85	2–3	Observed
3	0	25	1–2	Censored
3	0	25	1–3	Observed

Start time: time when become at risk of the transition event

Each row informs model for time to event of interest

Times to competing events treated as censoring

Multi-state models for continuous observation: software

Standard survival modelling software to estimate hazard of each transition, its dependence on time and other covariates

- `coxph()` fuction in `survival` package (Cox regression, semiparametric)
- `flexsurvreg()` or `flexsurvspline()` function in `flexsurv` package (fully parametric models)
- `survreg()` function in `survival` package

Specialised software then needed to deduce quantities needed for decision modelling: transition probabilities, expected total time spent in some state over some horizon...

- `mstate` (uses `coxph()` fit, can't extrapolate beyond data)
- `flexsurv` (fully-parametric, can extrapolate)
- Claire Williams' code (see following talk...)
- `multistate` in Stata (Crowther & Lambert)

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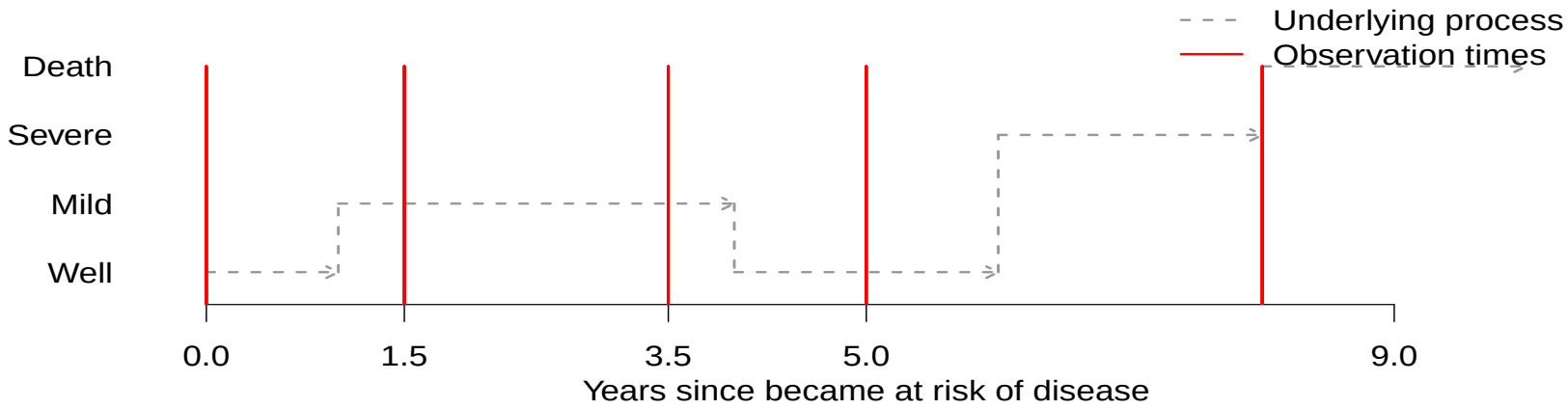
Multi-state models for continuous observation: resources

- de Wreede, L. C., Fiocco, M., & Putter, H. (2011). `mstate`: an R package for the analysis of competing risks and multi-state models. Journal of Statistical Software, 38(7), 1-30.
- Jackson, C. H. (2016). `flexsurv`: a platform for parametric survival modeling in R. Journal of Statistical Software, 70.
- Williams, Claire, et al. "Cost-effectiveness analysis in R using a multi-state modeling survival analysis framework: a tutorial." Medical Decision Making 37.4 (2017): 340-352.
- Stata `ssc install multistate`

Multi-state models for intermittently-observed data

Panel data: know state at finite number of observations



- Exact event times unknown $\rightarrow$ semiparametric or flexible parametric time-to-event models are infeasible
- Continuous-time Markov models with piecewise-constant transition rates can be easily fitted instead
- Can deduce transition probabilities over any discrete time interval, expected total time spent in a state over a horizon...

Multi-state models for intermittently-observed data: software and resources

`msm` package in R

- any state-transition structure, proportional-hazards models for covariates, piecewise-constant hazards over time...
- Jackson, C. H. (2011). Multi-state models for panel data: the `msm` package for R. Journal of Statistical Software, 38(8), 1-29.

Recommended textbook

- Van Den Hout, A. (2016). Multi-state survival models for interval-censored data. Chapman and Hall/CRC.

Using multi-state model results in cost-effectiveness analysis

Any of these multi-state models can give

- transition probabilities: $Pr(S(t+u) = s | S(t) = r)$ between states $S(t)$ for any discrete time interval u
  - could use to inform a state-transition decision-analytic model
- expected time $T_r(t)$ spent in each state r between now and some horizon t.
  - Define cost and utility for occupying state
  - $\rightarrow$ expected cost and QALY attributable to periods in that state
  - $\rightarrow$ sum over states to get total cost, QALY.
  - multi-state model is itself the (continuous-time) decision model

Partitioned survival analysis

Common in cancer HTAs

- Estimates progressed state occupancy from difference between progression-free, overall survival curves
- Less flexible than multi-state models (assumes independent endpoints, progression-only transition structures)

Discussion and critique

- `http://nicedsu.org.uk/technical-support-documents/partitioned-survival-analysis-tsd/`
- Williams, C., Lewsey, J. D., Mackay, D. F., & Briggs, A. H. (2017). Estimation of survival probabilities for use in cost-effectiveness analyses: a comparison of a multi-state modeling survival analysis approach with partitioned survival and Markov decision-analytic modeling. Medical Decision Making, 37(4), 427-439.

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Summary: continuous-time multi-state models

- With richer data comes need for richer models
- Continuous-time, individual-level multi-state data
  - deserve continuous-time multi-state models!
- Models with appropriate software and documentation
  - enable using available evidence more expressively
  - $\rightarrow$ models, decisions that reflect reality