Joint Modelling of Viral Kinetics and Influenza Symptoms

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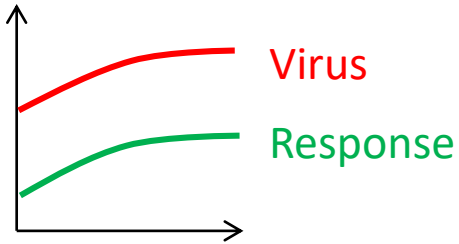
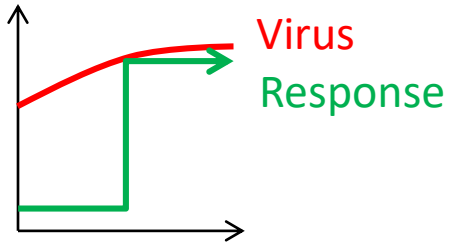
Roche Products ltd

Viruses and Symptoms

- Can we quantify the association between viruses and symptoms?
- Is virus titer a good biomarker for symptoms resolution?
  - A priori, virus IS the “perfect” biomarker
- Do patients that clear viruses faster also resolve symptoms faster?
- Does the immune system response gradually adapt to the severity of infection?





Challenge Studies

Carrat et al. (2018) Am J Epidemiol 2008;167:775–785

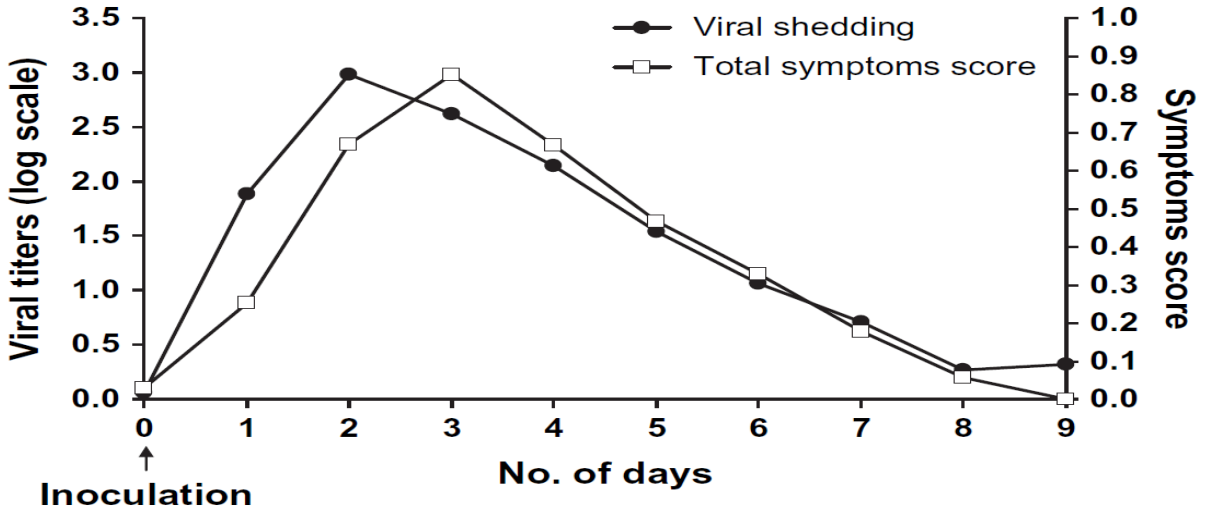
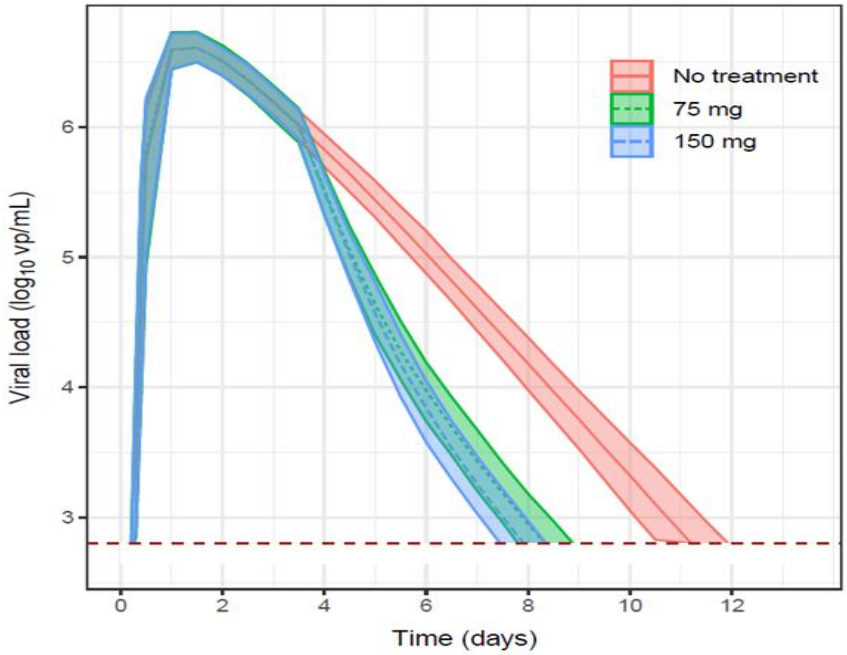


FIGURE 5. Summary curves of viral shedding and total symptoms scores in experimental influenza virus infection. Thirteen curves were used for viral shedding (refer to figure 2 legend), and 17 curves were used for total symptoms scores (refer to figure 3 legend).

Why Does it Matter (in Pharma)?

- Efficacy (not virology) is the primary outcome to patients, doctors and regulators
- Anti-virals act directly on viruses... What about symptoms?
- In small studies on immunocompromised (IC) paediatric patients, a disease model helped us extrapolating efficacy from a larger IC adults study (FDA Guidance)
- Disease model links drug exposure with virology but not symptoms
- Would regulators accept extrapolations more readily if a disease model linked exposure to symptoms?

Disease Model



Studies

WV15670

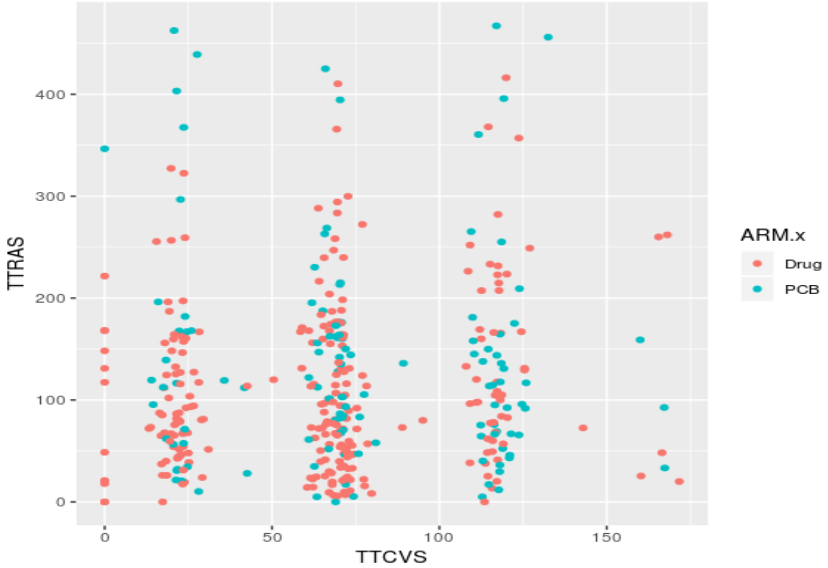
- Randomised, double blind, placebo-controlled, parallel arms* (75 mg b.i.d., 150 mg b.i.d.)
- Centers: 51 European, 11 Canadian, 1 Hong Kong
- OwH adults (18-65y)
- Completers: 223 PCB, 235 75mg, 230 150mg

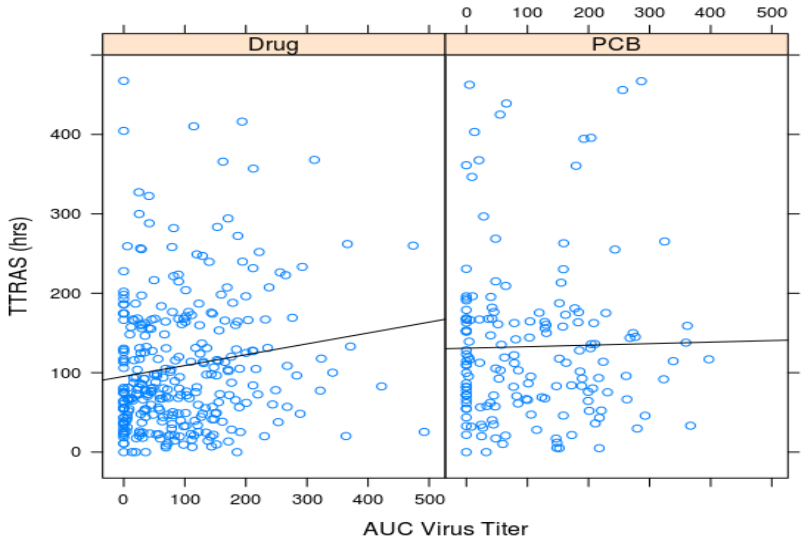
WV15671

- Randomised, double blind, placebo-controlled, parallel arms* (75 mg b.i.d., 150 mg b.i.d.)
- Centers: 57 US
- OwH adults (18-65y)
- Completers: 197 PCB, 194 75mg, 190 150mg

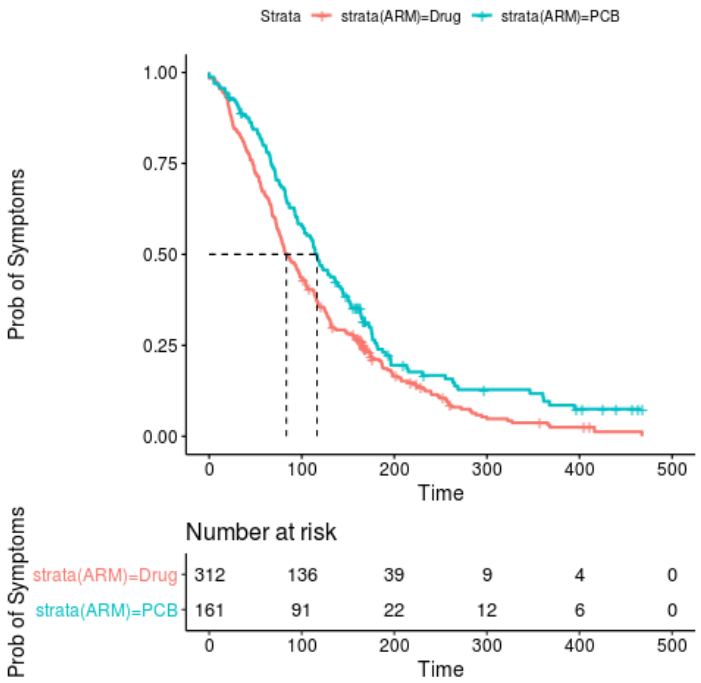
*Both treatment arms will be pooled as there were no differences in TTRAS or TTCVS

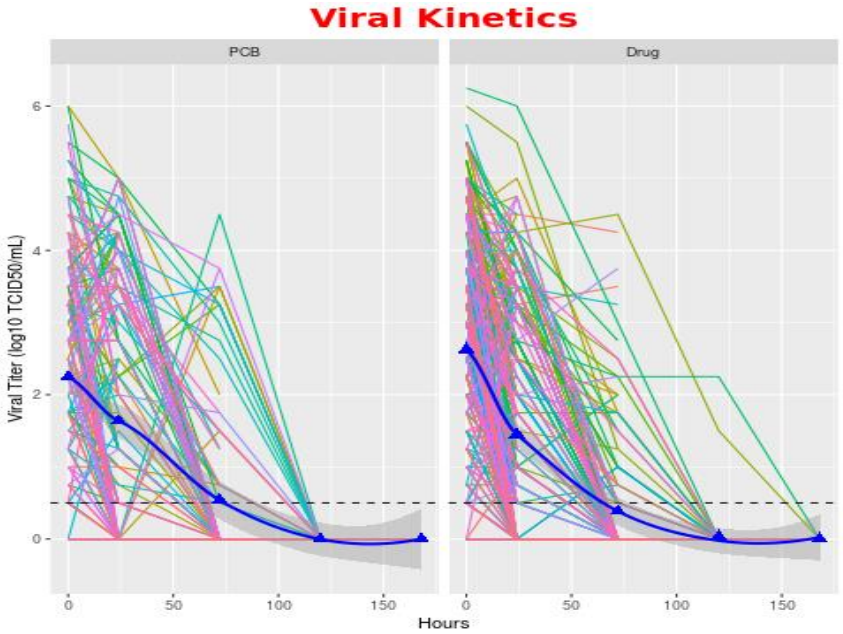
Visual Virus-Symptoms Associations





Symptoms Resolution - Viral Kinetics





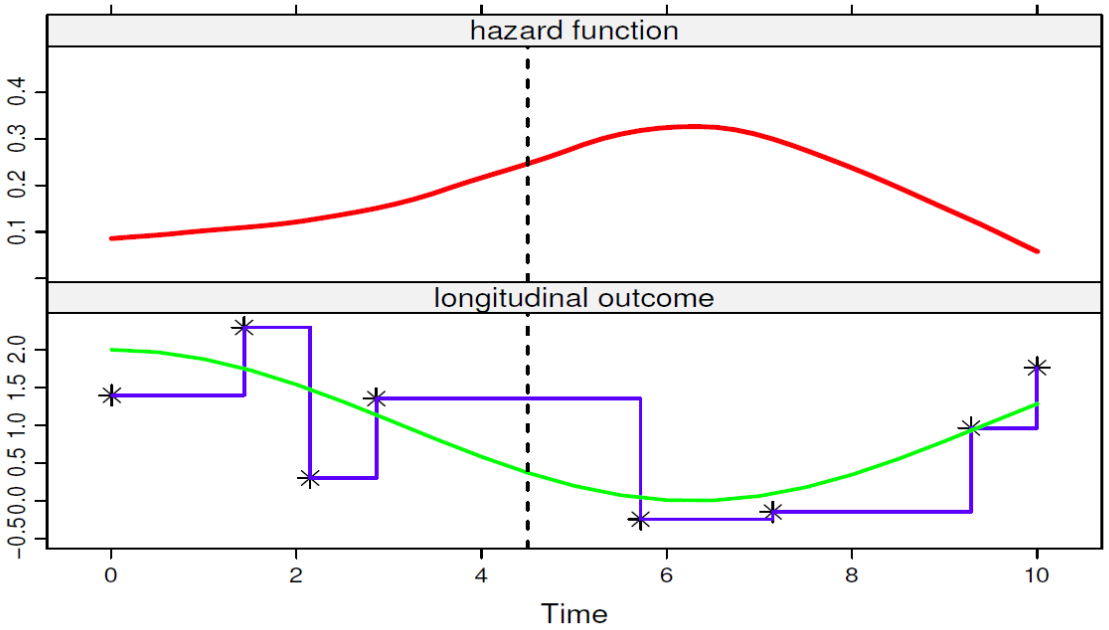
Time-dependent Cox Model

- Coxph(Surv(start,stop,event)~arm+virus,data)

Variable	HR (95% CI)	p
Drug	1.4 (1.1 to 1.7)	0.003
Virus	0.95 (0.9 to 1)	0.23

SUBJECT	ARM	RESULT	start	stop	TALLSYMP	event
<fct>	<fct>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>
1030	Drug	1.25	0	24	93.5	0
1030	Drug	0	24	72	93.5	0
1030	Drug	0	72	93.5	93.5	1
1031	Drug	3.75	0	24	25.2	0
1031	Drug	2.5	24	25.2	25.2	1
1033	PCB	3.5	0	24	182.	0

The key novelty of Joint Models



Rizopoulos 2018

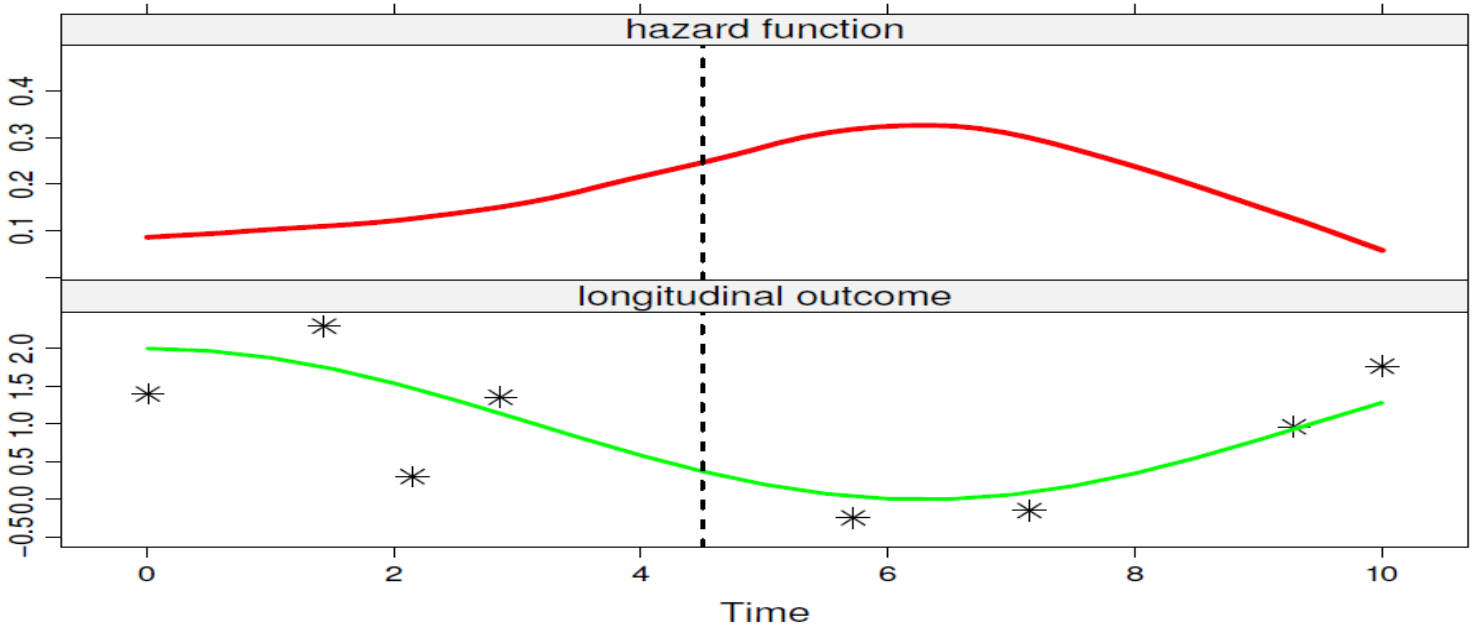
Flexibility of Joint Models

- **Instant effect**: Viral titer at time t, v(t), affects hazard at time t, h(t)
- **Lag**: v(t-lag) affects h(t)
- **Value and slope**: Titer, v(t), and slope, v’(t), affect h(t)
- **Random longitudinal parameters**: Slope of titer at time t, v'(t), affects h(t)
- **Cummulative**: unweighted AUC viral titer up to time t affects h(t)
- **Weighted Cummulative**: AUC viral titer up to time t affects h(t) but closer part affects more
- **Exogenous covariates**, e.g. weather

- **Stratified risks**, e.g. different hospitals or studies
- **Latent classes**, e.g. population heterogeneity
- **Competing risks**, e.g. recovery or death
- **Recurrent events**, e.g. symptoms rebound
- **Accelerated failure times**, e.g. non-PH
- **Categorical longitudinal outcomes** (GLMM), e.g. categorical biomarkers (low, medium, high)
- **Multiple longitudinal outcomes**, i.e. assumed independent

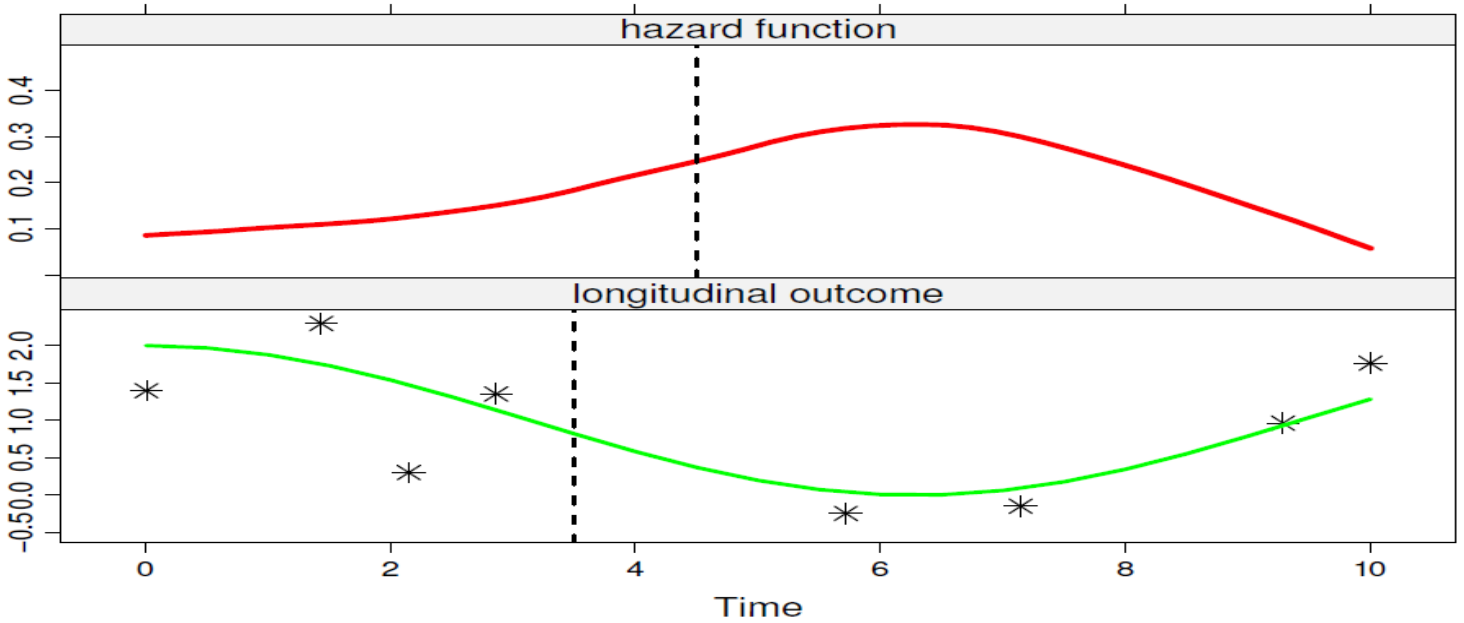
Symptoms | Virokinetics
Virokinetics
Virus History

$$h_i(t|V_i(t)) \sim h_0(t) exp\{\gamma' w_i + \alpha v_i(t)\}$$
$$y_i(t) \sim v_i(t) + \varepsilon_i(t) = x_i\ (t)\beta + z_i\ (t) b_i + \varepsilon_i$$
$$V_i(t) \sim \{v_i(s), 0 \leq s < t\}$$



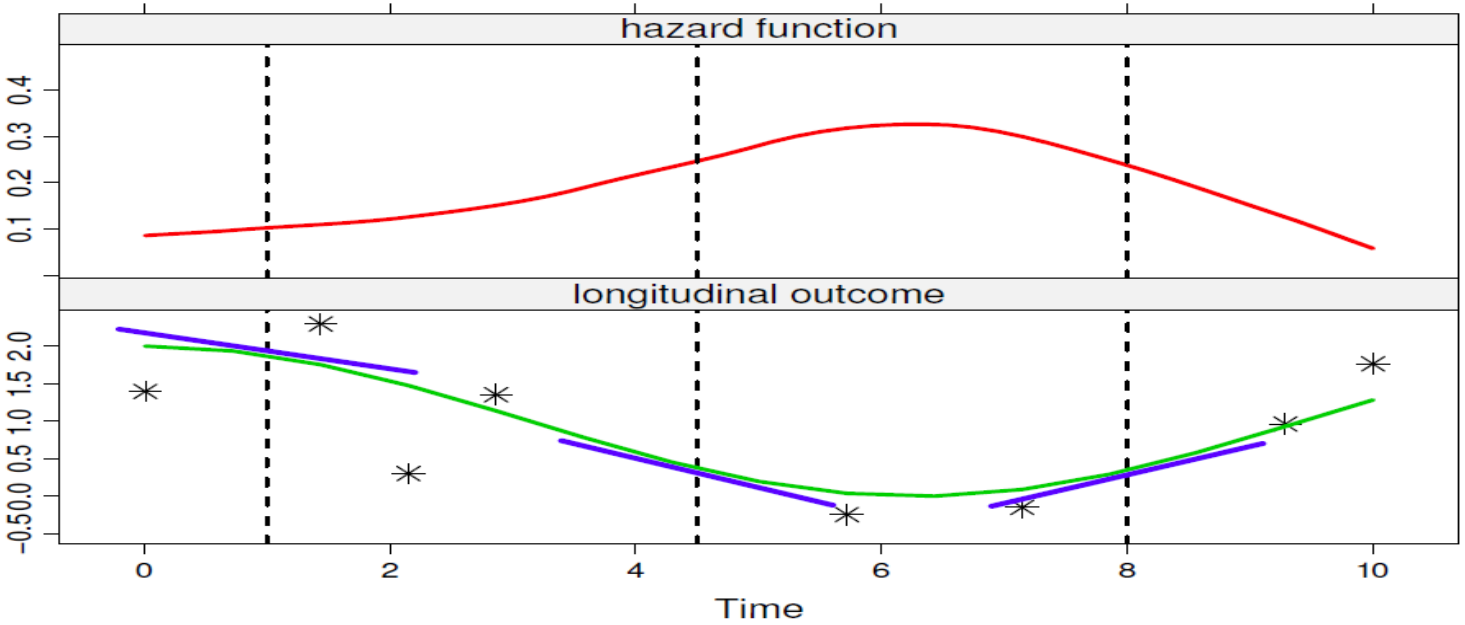
Rizopoulos 2018

$$h(t) \sim f\big(\boldsymbol{v}(t - lag)\big)$$



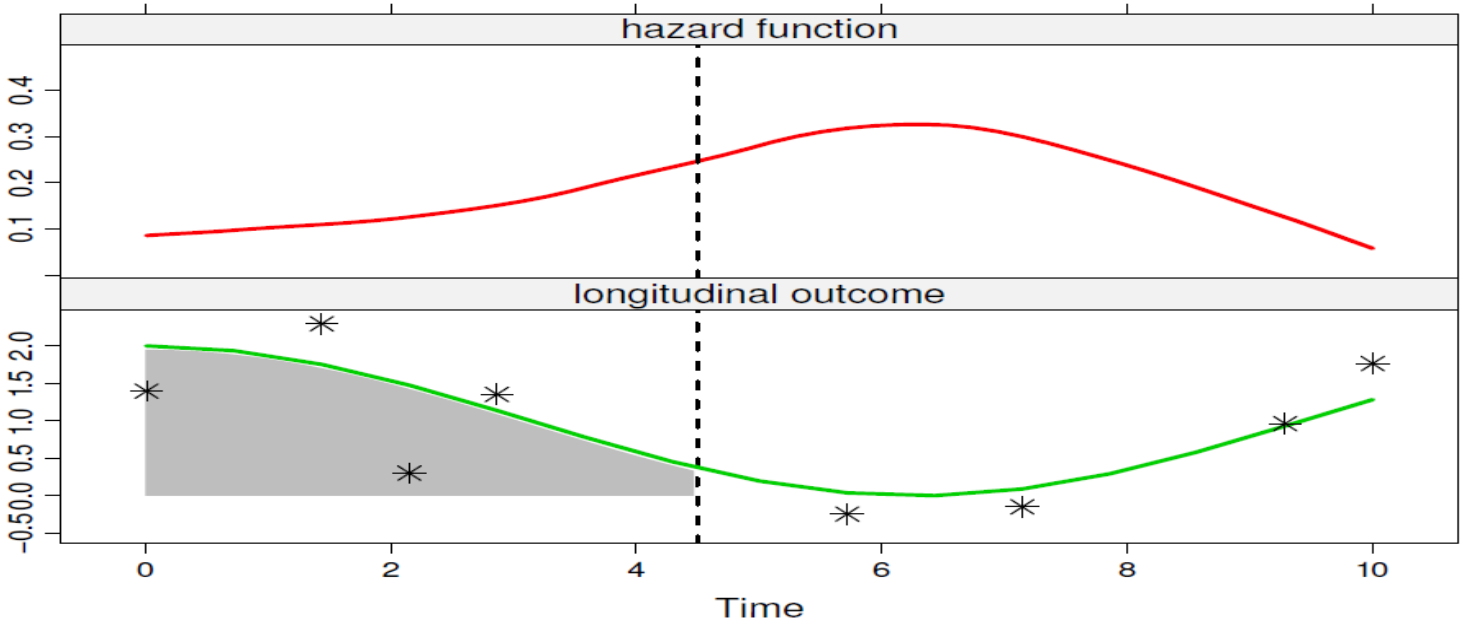
Rizopoulos 2018

$$h(t) \sim f\left(v(t), v'(t)\right)$$



Rizopoulos 2018

$$h(t) \sim f\left(AUC(t)\right)$$

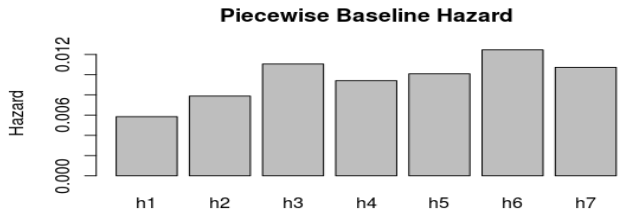


Rizopoulos 2018

Joint Model 1 (JM1)

- Virokinetics
  - $y = v + e = B_0 + B_1 T + B_2 T^2 + b_0 + b_1 T + e$
  - B_i = fixed effects; b_i = random effects
- Survival
  - $ttras \sim drug + e$
- Joint Model
  - $h_i(t) = h_0(t) e^{\alpha v + drug} + e$

- Baseline hazard:
  - Assumed piecewise constant PH
  - Alternatives:
    - Weibull-PH
    - Weibull-AFT
    - Cox-PH
    - Spline-PH
    - ch-Laplace



Joint Models 1: HR virus

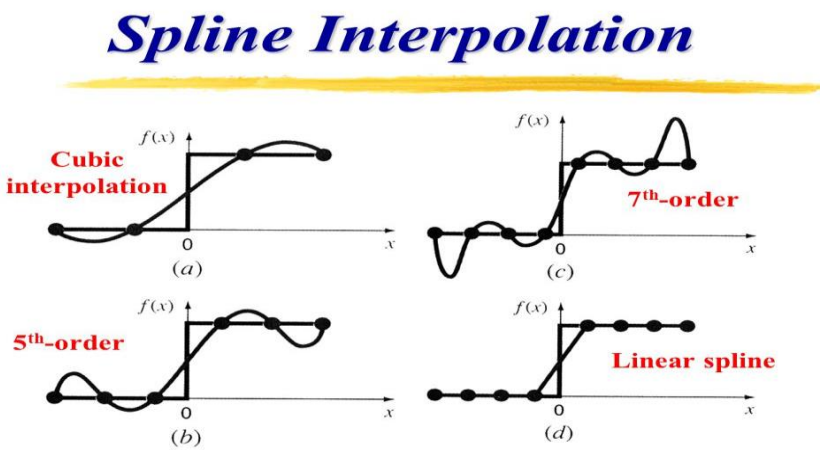
Model	HR (95% CI)	p	AIC
td-Cox	0.95 (0.87 to 1.03)	0.23	4428
JM1	0.95 (0.88 to 1.02)	0.15	9463
JM1: Lag-1h	0.95 (0.88 to 1.02)	0.15	9463
JM1: Lag-18h	0.94 (0.87 to 1.02)	0.12	9463
JM1: titer + slope	0.94 (0.87 to 1.01)	0.21	9462
JM1: Cum	1 (1 to 1)	0.23	9464
JM1: wt Cum	0.88 (0.75 to 1.02)	0.09	9462

N.B. AIC = 2k – 2logL; k=number estimated parameters; logL=log likelihood

The likelihood function of td-Cox and JM's are so different that it makes no sense to compare them

Joint Model 2 (JM2)

- Virokinetics
  - $y = v + e = spline(T, df = 2) + b_0 + b_1 T + e$
- Survival
  - $ttras = drug + e$
- Joint Model
  - $h_i(t) = h_0(t)e^{\alpha v + drug} + e$



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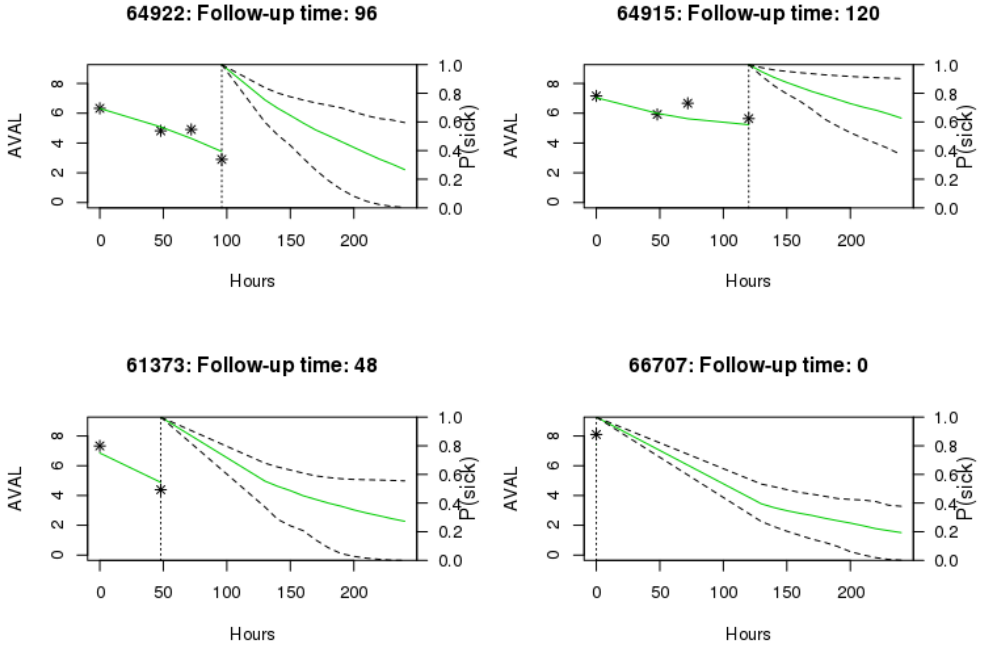
JM1: Cum	1 (1 to 1)	0.23	9464
JM1: wt Cum	0.88 (0.75 to 1.02)	0.09	9462
JM2	0.89 (0.79 to 1)	0.06	9454
JM2: Lag-1h	0.89 (0.79 to 1)	0.05	9454
JM2: Lag-18h	0.89 (0.8 to 1)	0.04	9454

Dynamic Predictions

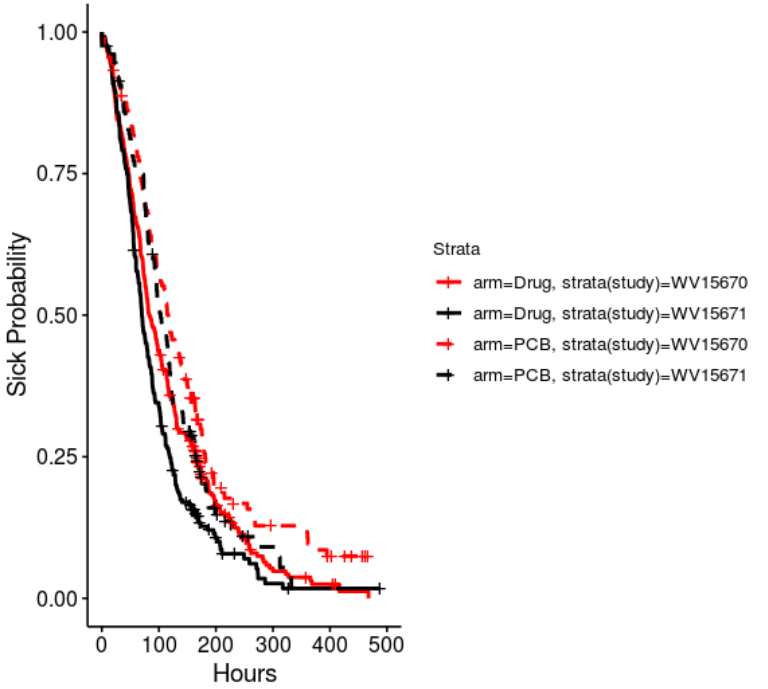


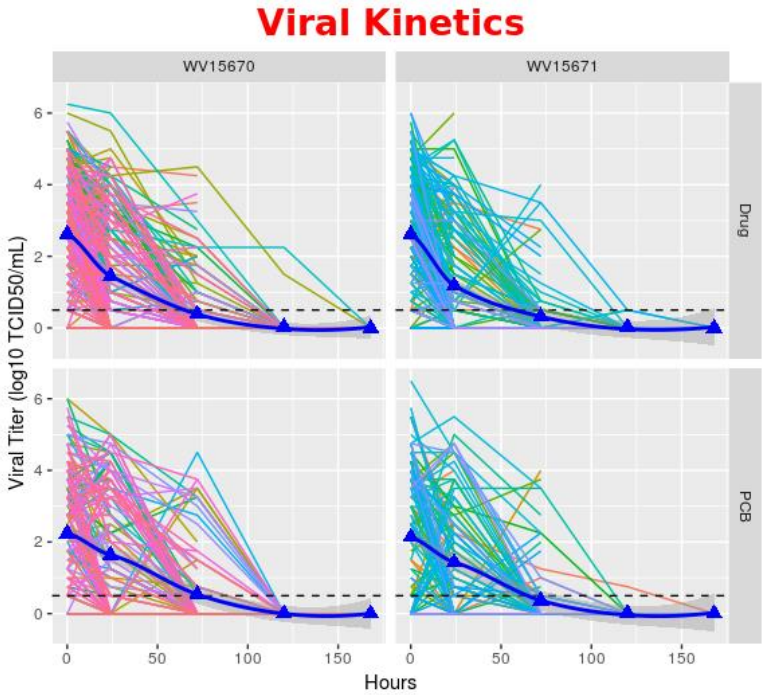
WV15671 (US)

Model	HR (95% CI)	p	AIC
td-Cox	0.99 (0.91 to 1.09)	0.89	3347
JM1	0.96 (0.88 to 1.05)	0.39	7303
JM1: Lag-1h	0.96 (0.88 to 1.05)	0.38	7303
JM1: Lag-18h	0.96 (0.88 to 1.06)	0.46	7303
JM1: titer + slope	NA	NA	NA
JM1: Cum	1 (1 to 1)	0.56	7303
JM1: wt Cum	0.87 (0.71 to 1.07)	0.18	7302
JM2	0.89 (0.76 to 1.05)	0.18	7291
JM2: Lag-1h	0.89 (0.76 to 1.05)	0.18	7291
JM2: Lag-18h	0.93 (0.8 to 1.08)	0.36	7292

Pooled Analysis

Type	HR	95% CI
Stratified	1.1	0.88 to 1.35
Unstratified	1.1	0.86 to 1.30

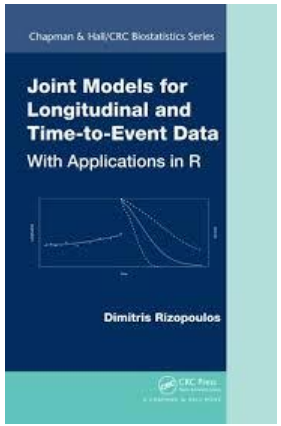


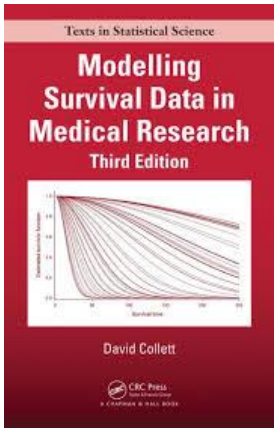


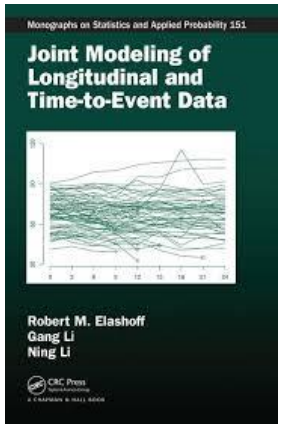
Conclusions

- It is hard to quantify the association between viral kinetics and symptoms resolution
- The strength of the association depends on the sophistication of the model (overfitting?)
- Maybe we need to measure covariates in the biological path connecting viruses with symptoms, e.g. white blood cells
- Although this research is not crucial for filing a new drug, it enhances our understanding of the disease biology and how the immune system fights diseases

Literature


Chapman & Hall/CRC Biostatistics Series
Joint Models for Longitudinal and Time-to-Event Data
With Applications in R
Dimitris Rizopoulos
CRC Press


Texts in Statistical Science
Modelling Survival Data in Medical Research
Third Edition
David Collett
CRC Press

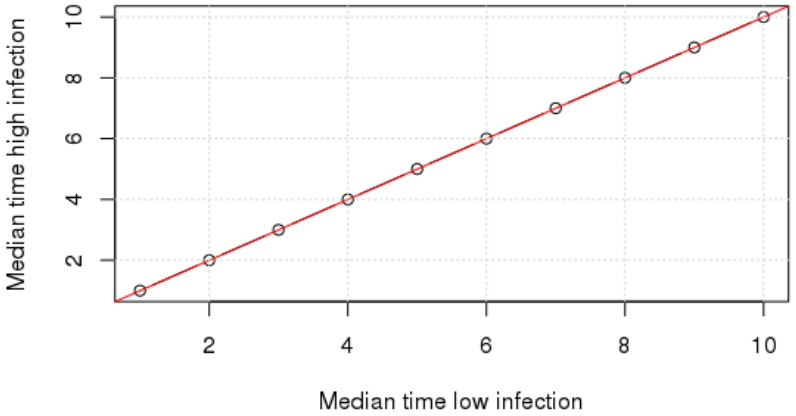

Monographs on Statistics and Applied Probability 151
Joint Modeling of Longitudinal and Time-to-Event Data
Robert M. Elashoff
Gang Li
Ning Li
CRC Press

Doing now what patients need next

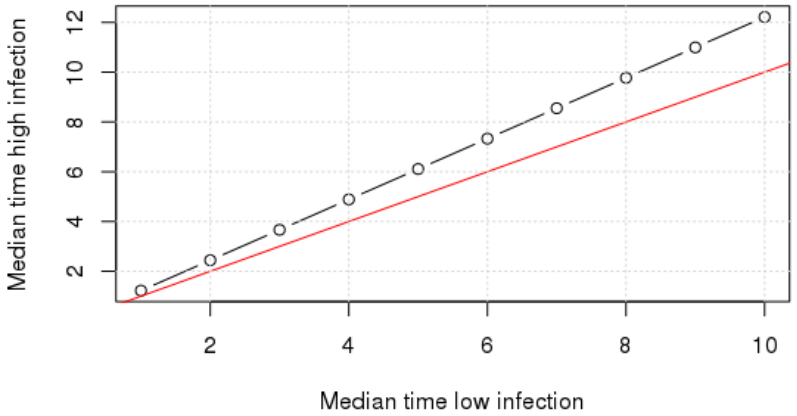
Back-ups

Predictions of resolution of all symptoms given association

- HR = 1 (α=0)

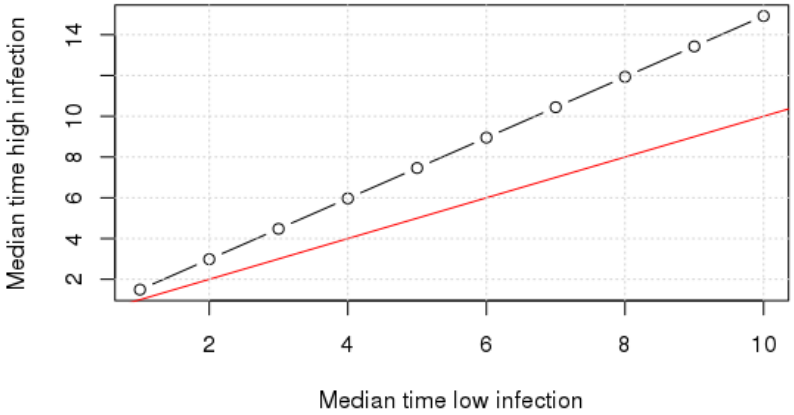


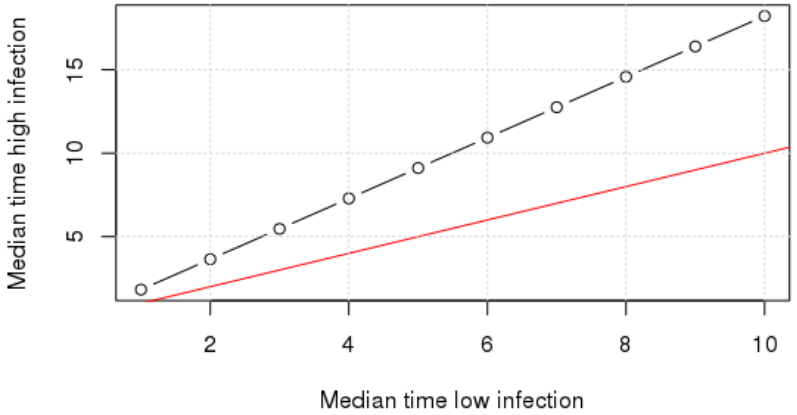
- HR = 0.95 (α=-0.05)



Predictions of resolution of all symptoms given association

- HR = 0.9 (α=-0.1)
- HR = 0.86 (α=-0.15)





Associations using splines to model baseline hazard

- Association

Knots	Linear	Quadratic	Cubic
0	-0.018	-0.090	-0.113
1	-0.050	-0.076	-0.095
2	-0.092	-0.105	-0.125
3	-0.124	-0.127	-0.127
4	-0.135	-0.130	-0.150
5	-0.157	-0.157	-0.131

- P-values

Knots	Linear	Quadratic	Cubic
0	0.754	0.059	0.001
1	0.383	0.335	0.194
2	0.004	0	0.002
3	0.105	0	0
4	0	0	0
5	0	0	0

Log-likelihoods of td-Cox and joint model

- Contribution to the logL of individual i to a joint model
- $logL_i(\theta) = log \int \left\{\prod_{j=1}^{n_i} p\left(y_{ij}\middle|b_i;\theta\right)\right\}\left\{h(T_i|b_i;\theta)^{\delta_i} S_i(T_i|b_i;\theta)\right\}p(b_i;\theta)db_i$
- Contribution to the logL of individual i to a td-Cox model
- $logL_i(\theta) = \delta_i \left\{\sum_{j=1}^{p} \beta_j x_{ji}(t_i) - log \sum_{l \epsilon R(t_i)} exp\left(\sum_{j=1}^{p} \beta_j x_{jl}(t_i)\right)\right\}$

How complex can the model be?

- Total number of parameters between 1/10 and 1/20 of events (Harrell 2001)

Main Assumption: conditional independence

- $p(y_1, y_2) = \int p(y_1|b)p(y_2|b)db$
- y_1 and y_2 are responses, e.g. both longitudinal, longitudinal and time-to-event…
- b unknown random effects

Doing now what patients need next