

A closed form solution set-point model of treatment response in multiple diseases

Daren Austin, Stefano Zamuner
Clinical Pharmacology Modelling and Simulation, GSK, UK



Introduction

The placebo response hypothesis

Many clinical trials demonstrate a profound placebo response once patients enter a clinical trial. The magnitude of this response may obscure detection of treatment signals and subsequently invalidate the trial.

Placebo response often appears to follow a trajectory consistent with treatment, implying modification of an underlying equilibrium process. A naive interpretation of this process is regression to the mean. An alternative interpretation might be that the action of entering the clinical trial causes a resetting of the dynamical process of disease presentation through intrinsic factors such as improved access to healthcare during a trial, continuous disease monitoring, better compliance to standard of care, etc.

We make two assumptions regarding disease progression during a clinical trial: First, that the timescale of the trial is less than the characteristic time for disease progression off treatment. Secondly the action of entering a clinical trial causes a disruption of the equilibrium state and that subsequent disease trajectories follow an approach to the new equilibrium (that may not be reached for relatively short trials). Finally we shall consider the case where no equilibrium is established and time-dependent disease progression is observed for the duration of the trial.

Model Assumptions

Disease is assumed to be characterised by a status variable $D(t)$ and characterised by general input and output processes of the form

$$dD(t)/dt = Kin - Kout D(t),$$

where Kin and $Kout$ represent production and loss terms for disease status. Both Kin and $Kout$ may be time-dependent depending on the disease and clinical trial. At entry into the trial we assume

- Disease status is at equilibrium $D(0) = Kin/Kout$.
- At least one of the disease turnover parameters is modified by entering the trial.
- Modification of parameters may be treatment- and time-dependent.

Assume that on entry into the trial $Kout$ is modified to a new value such that for patient i , and treatment j , $Kout^i = (1 + P_{ij}) Kout$, where P_{ij} denotes patient i 's response to treatment j after entering the trial. The new equilibrium for this patient is given by $Kin/Kout^i = Kin/Kout (1 + P_{ij})$ (Fig 1)

Fig 1: an example with closed-form solution

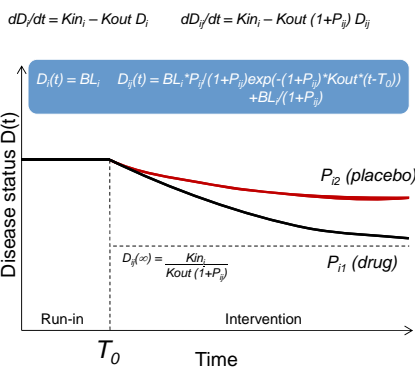
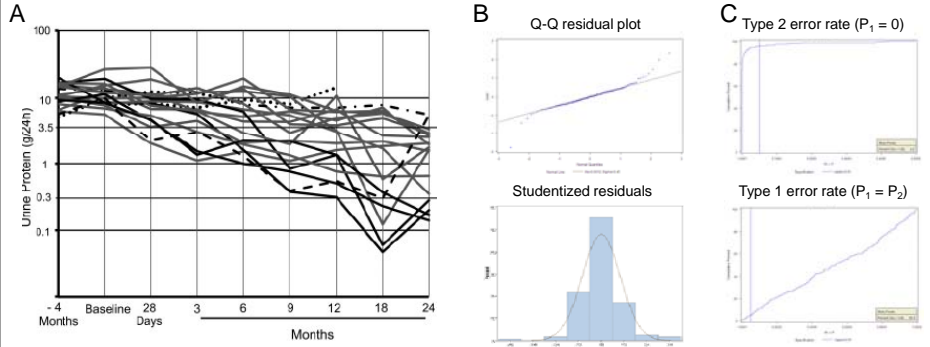


Fig 3: Effect of RTX on proteinuria in patients with IMGN



Parameter Estimates obtained from proc NLMIXED (SAS v9.2)									
Parameter	Estimate	Standard Error	DF	t Value	Pr > t	Alpha	Lower	Upper	Gradient
BL (g/24h)	10.4061	1.3873	18	7.50	<.0001	0.05	7.4914	13.3207	0.002364
P ₂ (Treat)	16.3693	5.0997	18	3.21	0.0049	0.05	5.6553	27.0833	-0.00014
Kout (1/d)	0.008321	0.002806	18	2.97	0.0083	0.05	0.002426	0.01422	0.74326
Omega1	10.4157	7.8608	18	1.33	0.2017	0.05	-6.0992	26.9307	0.000919
Omega2	120.25	76.6153	18	1.57	0.1339	0.05	-40.7100	281.22	-0.00393
EPS	0.4311	0.06177	18	6.98	<.0001	0.05	0.3013	0.5608	-0.0065

Model application 1: Proof of Concept trial analysis

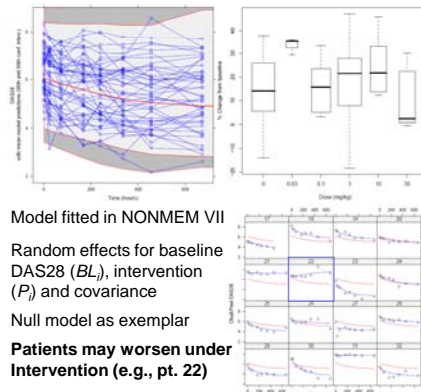
aOSM in Rheumatoid arthritis^[1]

In a Rheumatoid Arthritis proof of concept study, GSK315234A, a monoclonal antibody targeting OSM, was tested in single and multiple doses over a wide dose range. Disease activity score, DAS28, was used as an efficacy endpoint. Weighted mean DAS28 data was also estimated.

The closed form solution presented in Fig 1 was fitted to emergent data during the trial, and the weighted mean estimated using the integral of the closed-form solution. The effects of treatment were inferred using a variety of models:

- Null model (no treatment effect)
- Treatment as a class effect
- Treatment as dose response (parametric and non-parametric assumptions possible)

Fig 2: VPC and estimated weighted mean treatment effect (Null model)



Model fitted in NONMEM VII

Random effects for baseline DAS28 (BL_i), intervention (P_{ij}) and covariance

Null model as exemplar

Patients may worsen under Intervention (e.g., pt. 22)

The model provides a good interpretation of the data with limited evidence of treatment effect after single dose. Influence of treatment effects are tested directly

Model application 2: Inference of placebo effect

Rituximab in IMGN^[2]

In an open-label, uncontrolled study of rituximab in idiopathic membranous glomerulonephropathy (IMGN), 20 patients were successfully treated for a period of up to two years^[2] (Fig 3A). Since the study was uncontrolled, we wanted to make inference of the magnitude of a possible placebo response.

The closed form solution was fitted to individual subject data (Fig 3B and table), using proc nlmixed (SAS v9.2) and placebo response inferred by adjusting the magnitude of treatment parameter P_{ij} accordingly for subsequent trial simulation. A repeated measures analysis of simulated patient profiles for $N = 80$ patients with observations at 0, 1, 3 and 6 months was conducted to evaluate Type 1 and 2 error rates assuming placebo has no effect (T_2) and an RTX-like effect (T_1) respectively (Fig 3C).

Model extension : Time dependence

The model is easily extended to the time-dependent case, where loss of response is accommodated: Let $Kin(t)$ increases linearly with time; $Kin(t) = Kin (1 + \alpha t)$, patients enter the trial at time $t = 0$ with $D(0) = \beta BL$, and intervention begins at time T_0 as before,

$$D(t) = BL(1+\alpha t) - BL(\alpha/Kout)(1-\exp(-Kout t)) + (\beta - 1) BL \exp(-Kout t) \quad 0 < t \leq T_0$$

$$D(t) = BL(1+\alpha t)(1+P) - BL(\alpha/Kout)(1+P)^2 + BL(1+\alpha T_0)(P/(1+P)) - (\alpha/Kout)(1-\exp(-Kout(T_0-t)) - 1/(1+P)^2 + (\beta - 1) \exp(-Kout(T_0-t))) \exp(-Kout(1+P)(t-T_0)) \quad t > T_0$$

Setting $\alpha = 0$ and $\beta = 1$ recovers the original model

Conclusion

A simple set-point model describes short-term disease progression under treatment. After validation in various settings the model is used for inference and model-based trial design. The closed form solution makes implementation straightforward in SAS and NONMEM

References

1. Zamuner et al. PK-PD modelling of aOSM in RA patient study including exploration of carrier protein effect. PAGE abstract (2012).
2. Fervenza et al. Rituximab treatment of IMGN. Kidney International (2008) 73: 117 - 125.

Acknowledgements

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