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Indirect Response Models with Positive Feedback: Equations, Properties, and Possible Applications

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Poster: Methodology- Other topics

Background: Flare-ups, a characteristic feature of a number of autoimmune diseases is sudden worsening of the disease with a very slow resolution of symptoms. Triggers of the flares, when known, are usually external challenges of short duration (infection, stress, exposure to allergen, skin trauma, etc). Similarly, there are instances when short treatment interventions produce long-lasting effects. Known mechanistic pharmacodynamic (PD) models postulate that the system returns to the baseline state soon after the intervention is stopped. These models cannot describe flare-ups or long lasting effects of short treatments.

Objectives: To propose a new type of PD models for description of systems (biomarkers) with non-unique steady-state or quasi-steady-state solutions, and to suggest possible applications of these models.

Methods: The following indirect response model with positive feedback introduced through the transit compartment (A_2) is proposed for the biomarker (A_1):

$dA_1/dt=K_{IN}-K_{OUT}A_1+K_{FB}\ (f_2(C)A_2-f_1(C)A_1)$ and

$dA_2/dt=K_{TR}\ (A_1-A_2)$.

Here K_{FB} and K_{TR} are the feedback and transit compartment rate constants; f_1 and f_2 are non-negative functions of the intervention level C (e.g. drug concentration) such that $f_1(0)=f_2(0)=1$.

In this system, production (K_{syn}) and elimination rate (K_{deg}) of the biomarker are represented by

$K_{syn}= K_{IN}+K_{FB}\ f_2(C)A_2$ and $K_{deg}= K_{OUT}+K_{FB}\ f_1(C)$.

Similarly to the indirect response models [1], four types of intervention were investigated: stimulation of production or elimination (f_2 or f_1 increases with C) and inhibition of production or elimination (f_2 or f_1 decreases with C). An investigation started with the limiting case $K_{IN}=K_{OUT}=0$, and was then extended to more general models. Stimulation of elimination (e.g. short drug treatment) was studied in details. All the other cases were similar.

Results: In the limiting case of $K_{IN}=K_{OUT}=0$ and in the absence of the external intervention ($C=0$), the system has infinite number of steady-state solutions. When disturbed by stimulation of elimination ($f_1(C)>1$), the biomarker level decreases, then increases, and stabilizes at a new steady-state level. This level is lower than the initial state, but higher than the minimum level achieved following the intervention. When K_{IN} and K_{OUT} are not zero, the biomarker follows a similar pattern. However, instead of the new steady-state level, it reaches the quasi-steady state that slowly returns the system back to the initial state. Inhibition of elimination reverses the pattern. Stimulation and inhibition of the biomarker production result in qualitatively similar patterns.

Conclusions: A new type of indirect response models with positive feedback allows the description of the systems where short-term interventions (treatments or triggers of the disease) lead to long-term effects and slow return to the pre-intervention state. The proposed models are physiologically meaningful in the context of autoimmune diseases, where breakdown of control mechanisms leads to chronic inflammation in response to activation of the immune system.

References:

[1] Dayneka NL, Garg V, Jusko WJ. Comparison of four basic models of indirect pharmacodynamic responses. J Pharmacokinet Biopharm. 1993 Aug;21(4):457-78.

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