Indirect Response Models with Positive Feedback: Equations and Possible Applications

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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, clinical effects, disease manifestations) 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 the positive feedback introduced through the transit (delay) compartment (A_2) is proposed for the biomarker (A_1):

$$\frac{dA_1}{dt} = K_{SYN} - K_{DEG} A_1, \qquad \frac{dA_2}{dt} = K_{TR}(A_1 - A_2),$$

where $K_{SYN} = K_{IN} + K_{FB} f_2(C) A_2$ is the biomarker production rate

$K_{DEG} = K_{OUT} + K_{FB} f_1(C)$ is the biomarker degradation rate

K_{IN} and K_{OUT} are the biomarker production rate and elimination rate constant independent of feedback,
K_{FB} and K_{TR} are the feedback and transit compartment rate constants,
$f_1(C)$ and $f_2(C)$ are non-negative functions of the intervention (drug concentration) C.

When K_{FB}=0, the model corresponds to the classical indirect-response model.

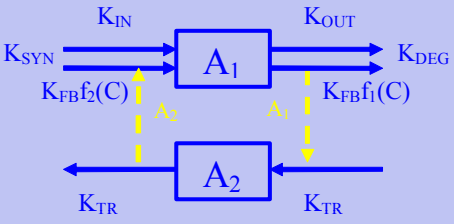
Similarly to the indirect response models [1], four types of intervention were investigated: stimulation of production or elimination (f_2 or f_1 increases with C) and inhibition of production or elimination (f_2 or f_1 decreases with C). First, the special case $K_{IN} = K_{OUT}$=0, and then more general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

Results: In the case $K_{IN} = K_{OUT} = 0$ 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 (Figure 1, upper left). 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 the concentration 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 biomarker production result in a 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. Journal of Pharmacokinetics and Biopharmaceutics 1993 Aug; 21(4): 457-78.



Example: Stimulation of elimination

A number of autoimmune diseases are characterized by overproduction of a cytokine. Drug intervention inhibits cytokine signalling, and leads to decrease in the level of the cytokine

Drug Concentration (PK):	C = Dose exp(- K_{EL} Time)
Effect (PK-PD):	$Eff = E_{MAX}\, C/(EC_{50}+C)$
Cytokine level (A_1):	$dA_1/dt = (K_{IN} + K_{FB}\, A_2) - (K_{OUT} + K_{FB}\, (1+Eff))\, A_1$
Positive feedback with delay:	$dA_2/dt = K_{TR}(A_1 - A_2)$

Special case: $K_{IN} = K_{OUT} = 0$ (neutral equilibrium)

When drug concentration is equal to zero, the steady-state equations are:

$K_{FB}\,(A_2 - A_1) = 0$ and $K_{TR}(A_1 - A_2) = 0$. They are satisfied for any $A_1 = A_2$.

Any input (drug administration) shifts the system from one equilibrium state to another equilibrium state (Figure 1, upper left).

When K_{IN} and K_{OUT} are not zero, the system slowly returns to the baseline conditions (Figure 2, upper left).

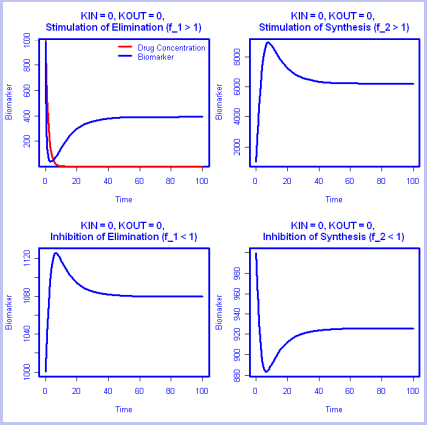


Figure 1: Simulated biomarker time course: K_{IN}=0, K_{OUT} =0

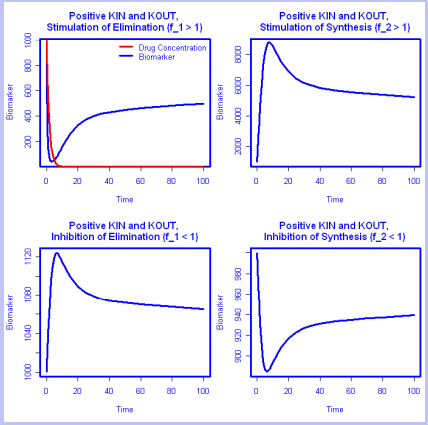


Figure 2: Simulated biomarker time course: general case (K_{IN}>0, K_{OUT}>0)

Example: Stimulation of biomarker production (flare-up) followed by stimulation of elimination (drug intervention)
External challenge (e.g. infection) stimulates the production of a biomarker by activation of the immune response. In healthy subjects, internal feedback mechanisms return the system to the normal state after suppression of the infection. In patients with damaged control mechanisms, the system (biomarker levels) would stay elevated unless forced to decrease by drug intervention.

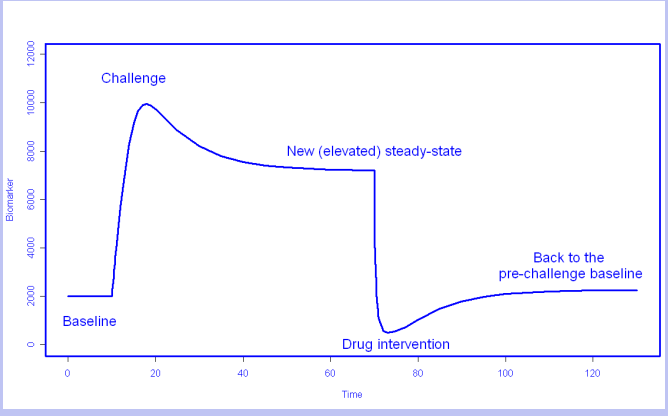


Figure 3: Simulated biomarker time course: disease flare-up followed by drug intervention

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