A mathematical model for endotoxin tolerance

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The endotoxin tolerance is a component of the innate immunity system. The actors of the endotoxin tolerance are: the endotoxin (LPS) and a representative cytokine, TNF-α.
Let us describe the experiment of endotoxin tolerance in a more specific way.
First step:
i. At (the initial) time t_0 the TNF-α concentration is measured; let it be α_0.
ii. Exposure to the LPS challenge; say of concentration β_0.
iii. At the time $t_1 > t_0$ the TNF-α concentration is measured again; one finds $\alpha_1 > \alpha_0$ (with the difference being quite significant).
iv. At the time $t_2 > t_1$ the TNF-α and LPS concentrations are measured; for TNF-α one obtains α_0 (or very close to it) and for LPS a concentration very close to 0.
The second step:
v. At the time t_2 (or very close after) a new exposure to the LPS challenge is considered (the concentration is the same, β_0.
vi. After the same time interval of (iii) the TNF-α concentration is measured. The (surprising) result is that, this time, the concentration is close to α_0. We consider the conclusion as being surprising because the system is in the same (TNF-α) initial condition as in the first step and is perturbed in the same way. This comes in contradiction with a deterministic autonomous TNF-α -LPS system. The experiment stops here but it is known that after some time the ability of reacting as in the first step is regained (if nothing "abnormal" happened).
After 2006, in a series of papers, Flondor, Olteanu and Vasilescu (cf. Bibl) have developed an original mathematical model for the endotoxin tolerance. The model is a generalized version of Michaelis-Menten-Hill differential system. The new basic idea is the existence of a TNF-α inhibitor. The equations are:

$$\frac{dx}{dt} = A(t)\ D_1\ \frac{x^n + E_1^n}{x^n + 1}\frac{1}{F_1 y + 1} - x$$

$$\frac{dy}{dt} = A(t)\ F_2\ \frac{y^m + E_2^m}{y^m + 1} - D_2(t)y$$

The notations are: $x, y, A(t)$ are the concentrations of TNF-α, of the inhibitor and of the endotoxin LPS, respectively. The coefficients of the sys-

tem, D_1, E_1, F_1, D_2, E_2 and F_2 are functions of time. We note that the system is a nonlinear and non autonomous differential system. In the medical literature there are data of the concentrations of x, y and $A(t)$ in in vivo and in vitro experiments. By using these data, we reproduced in silico these experiments and we obtained specific values of the coefficients. These values correspond to real clinical scenarios.

Refferences

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