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Adaptive Control: a Strategy to Treat Autoimmunity

BERNHARD SULZER AND J. LEO VAN HEMMEN*

Theoretical Biology and Biophysics, Los Alamos National Laboratory, Los Alamos, NM 87545, *U.S.A.*

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Anti-idiotypes of (natural) autoantibodies participate in the regulation of autoantibodies, their idiotype. Focusing on an idiotype/anti-idiotype pair embedded in an environment such as the central immune system, we start with the experimental fact that the level of anti-idiotypes is low in autoimmune patients but high in healthy individuals, and present a quantitative model. This is then used to develop an adaptive control strategy that induces a transition back to the tolerant, healthy, state and thus offers a vista of treating autoimmune diseases caused by the failure of idiotypic control of autoreactive B cells. The idea is to introduce an antigen or anti-idiotype that binds to the autoantibodies with high affinity, and to determine whether or not a fixed dose is to be injected depending on the autoantibody titer exceeding or not exceeding a threshold. Quantitative criteria are provided. The procedure is the more adaptive in that monitoring the autoantibody titer need only happen every x-th day where x can greatly exceed one. Adaptive control turns out to be robust. The arguments presented here also give a quantitative explanation of why the antigen–autoantibody interaction has to be specific so as to induce a backward transition and why an IVIg treatment therefore does not lead to a permanent improvement.

1. Introduction

An estimated 5% of the adults in Europe and North America suffer from autoimmune diseases. Substantial research efforts have been devoted to the development of therapies to suppress these misguided reactions of the immune system. Of course, a thorough understanding of the disease's causes would greatly facilitate its treatment. Taking advantage of a model based on experiments, we propose an *adaptive* strategy suited to treat autoimmune diseases caused by the failure of idiotypic control of autoreactive B cells. Adaptive control turns out to be extremely robust.

Anti-idiotypes of (natural) autoantibodies (Shoenfeld & Isenberg, 1993) participate in the regulation of autoantibodies (Zouali & Eyquem, 1983; Glotz & Zanetti, 1986; Miller *et al.*, 1992; Hurez *et al.*, 1993). Deficient idiotypic regulation of autoantibodies has been held responsible for a number of autoimmune diseases such as systemic lupus erythematosus (Segal *et al.*, 1994; Zouali, 1993), autoimmune thyroiditis (Tang *et al.*, 1992; Dietrich *et al.*, 1993), systemic vasculitis (Jayne *et al.*, 1993), the Guillain-Barré

* Author to whom correspondence should be addressed. Present and permanent address: Physik Department, TU München, D-85747 Garching bei München, Germany. E-mail: lvh@Physik.TU-Muenchen.de

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syndrome (Lundkvist *et al*., 1993), and anti-factor VIII:C (antihemophilic factor) autoimmune disease (Rossi *et al*., 1989; Sultan *et al*., 1991). Generally, autoimmune patients show a large ratio of autoantibody to anti-idiotype concentration whereas this ratio is small in healthy controls (Lundkvist *et al*., 1989; Sultan *et al*., 1987). Moreover, kinetic data of the autoantibody and its anti-idiotype concentration shows a reciprocal relationship pointing to dynamic interactions between them (Jayne *et al*., 1993).

The elevated level of anti-idiotypes in healthy individuals as well as in spontaneously recovered patients (Lundkvist *et al*., 1989, 1993; Sultan *et al*., 1987) suggests that increasing the anti-antibody concentration may be a promising route towards cure. Indeed, administration of intravenous immunoglobulins (IVIg) has proven beneficial in several autoimmune diseases (Dietrich *et al*., 1992) in that the autoantibody titer is reduced. IVIg treatment consists of intravenous injection of IgG which has been pooled from the serum of some ten thousands of healthy individuals, the rationale being that the pooled IgG would be enriched in anti-idiotypes. Although the improvement of the autoimmune condition due to IVIg treatment may be significant, it is always only transient.

Previous work (Sulzer *et al*., 1994) has led us to the conclusion that the limited success of IVIg treatment may be due to a lack of specificity of the pooled IgG. Here we evaluate the idea to employ *specific*, *high-affinity* anti-antibodies (in fact, any antigen which is recognized by/immunogenic for the autoantibodies) as therapeutic agents. Furthermore, our strategy is an *adaptive* one relying solely on the periodic measurement of the autoantibody titer as a criterion to determine whether or not the therapeutic agent should be administered.

2. Modeling B-cell Mediated Autoimmunity

To define the model we are working with we have to make a small detour and specify the equations which describe its dynamics. The population of large B cells of the clone i decays at a rate of d_B and grows at a rate modulated by a cross-linking stimulus h_i. Antibodies are produced by B cells at a rate $p_a k_d f_d(h_i)$, where f_d saturates for high stimulus values, and they disappear at rates d_A due to natural decay and $b_A h_i$ because of complex formation. We measure the concentrations of antibody, A_i in μg ml^{-1} and those of large B cells, B_i, in terms of cell ml^{-1}. Starting with a full-blown description including plasma cells and small lymphocytes we could show (Sulzer *et al*., 1994) that a simple set of two equations for B cells and antibodies in general suffices,

$$\dot{B}_i = [f^*(h_i) - d_B]B_i, \tag{1}$$

$$\dot{A}_i = p_a k_d f_d(h_i)B_i - [d_A + b_A h_i]A_i. \tag{2}$$

Here an overdot denotes a differentiation w.r.t. time and f^* is an effective dose-response function that is taken to be a log-bell-shaped curve

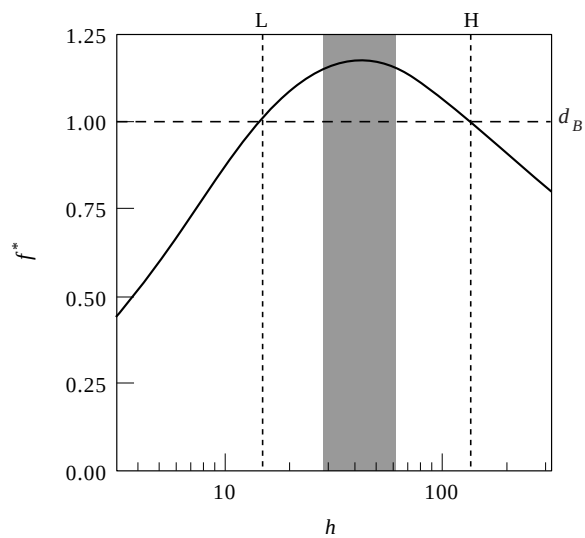

FIG. 1. Effective dose-response function f^* plotted against the logarithm of the stimulus, or field, h. The function is the difference of a saturating proliferation $f_p(h) = h/(h + \vartheta_p)$ and a saturating differentiation $f_d(h) = h/(h + \vartheta_d)$ so that $f^*(h) = k_p f_p(h) - k_d f_d(h)$ is a log-bell-shaped curve (Celada, 1971, 1992; Dintzis *et al*., 1976, 1982; Vogelstein, 1982; Goldstein, 1988; Metzger, 1992); the present argument does not depend on the logarithmic scale, though. Proliferation starts at a lower value of h than differentiation (i.e. $\vartheta_p < \vartheta_d$). There are two fixed points of eqn (1), H(igh) and L(ow), which are such that $f^*(h) = d_B$, i.e. where (- - -) intersects the graph of f^*. The therapy aims at forcing $h_c \approx A_b$ to stay within the *stimulative range* of f^* centered at its maximum (shaded area). More precisely, the maximum is located at $h_{max} \approx \sqrt{\text{HL}}$ so that $\ln h_{max} = (\ln \text{H} + \ln \text{L})/2$ is at the center of the shaded area. The parameters are: $k_d = 1.5$ day^{-1}, $k_p = 2.0$ day^{-1}, $d_B = 1$ day^{-1}, $\vartheta_d = 100 = \mu$g ml^{-1}, and $\vartheta_p = 10$ μg ml^{-1}.

(Celada, 1971, 1972; Dintzis *et al*., 1976, 1982; Vogelstein *et al*., 1982; Goldstein, 1988; Metzger, 1992); cf. Fig. 1. In fact, any bell-shaped curve would do in the argument below.

If there were just a single pair consisting of an autoreactive clone b interacting with its anti-idiotype c, a self-antigen (u_b) and a foreign antigen (V) coupling to A_b, then the cross-linking stimuli of b and c are given by $h_b = A_c + u_b + V$ and $h_c = A_b$. We suppose that V decays proportionally to A_b,

$$\dot{V} = -k_e A_b V. \tag{3}$$

We assume implicitly that T cell help is available whenever it is needed. This assumption places the entire burden of controlling the autoantibodies on the idiotypic "network", viz., a pair of idiotype and anti-idiotype. In passing we would like to point to a recent note (Bona, 1998) emphasizing the suitability of anti-idiotype fragments for vaccination. In the present context, one could use the anti-idiotype c (or a fragment thereof) instead of the antigen V coupling to A_b. In the discussion below we subsume all these stimulatory agents under the name "antigen".

We now turn to the topology of the central immune system (Coutinho, 1989; Stewart & Varela, 1989; Sulzer *et al*., 1994), into which the above and other pairs have been embedded. On the basis of binding assays of Holmberg *et al*. (1984) and Kearney *et al*. (1987) all these pairs are assumed to interact with a large core population $\mathscr{A}$ whose clones interact with *all* clones, including themselves, though their affinity η is much less than that among the specific clones b and c. One obtains the complete equations by simply adding $\eta\Sigma_{i\in\mathscr{A}}A_i := \eta A_{\mathscr{A}}$ to the right-hand side of h_b and h_c and by defining the stimulus of an $\mathscr{A}$ clone through $h_a = A_{\mathscr{A}} + \eta(A_b + A_c)$. In the present context, then, we study a *specific* b–c pair coupled to the *polyreactive* $\mathscr{A}$ core.

It can be shown that the above system possesses an *autoimmune* state, a *tolerant* state, and a *neutral* state as fixed points of eqns (1) and (2); for an extensive discussion of the underlying mathematics we refer to Perelson & Weisbuch (1997). In the autoimmune state the autoreactive clone b is susceptible to stimulation and has a large antibody titer in contrast to its anti-idiotype c which has a low antibody level. Conversely, in the tolerant state A_c is large and suppresses clone b whose antibody concentration is low. The neutral state, finally, is characterized by the absence of both b and c. Most importantly, we find that specific, high-affinity autoantibodies need to be suppressed by specific, high-affinity anti-antibodies—in agreement with experimental results (Lundkvist *et al*., 1993). The need for specific idiotypic control is also consistent with the fact that specific, high-affinity antibodies dominate in autoimmune diseases while polyreactive, low-affinity antibodies are abundant in healthy individuals (Zouali, 1993; Souroujon *et al*., 1988).

Within the framework of our model (Sulzer *et al*., 1994), induction of autoimmunity can be explained by an antigen-induced transition from the tolerant to the autoimmune state. This suggests that the induction of a reverse transition from the autoimmune to the tolerant state may

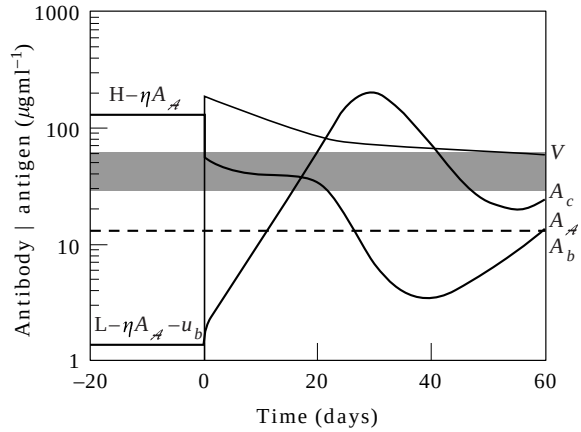

FIG. 2. At time $t = 0$ an antigen (coupling to the autoantibodies) at dose $V = 190\ \mu$g ml^{-1} is injected into the autoimmune state ($A_b \gg A_c$) of the system. One finds the labels A_c and A_b for the antibodies and autoantibodies (anti-idiotype and idiotype) on the right of the figure. The injection triggers a transition from the autoimmune to the healthy tolerant state. Note that A_b remains almost constant within the stimulative range of f^* (cf. Fig. 1) which allows clone c to grow at nearly optimal rate. A_b starts to decrease once it is surpassed by A_c. The plateau behavior is essential for a successful transition and can be obtained only for a very narrow range of antigen doses—here $180 < V(0) < 218\ \mu$g ml^{-1}. In colloquial terms, this would be luck and not wisdom so that a more systematic approach as in Fig. 3 is needed. The parameter values are as in Fig. 1 and $p_a = 0.1\ \mu$g cell^{-1}, $d_A = 0.2$ day^{-1}, $b_A = 0.1$ ml μg^{-1} day^{-1}, $k_e = 0.01$ ml μg^{-1} day^{-1}, $\eta = 0.05$, and $u_b = 7\ \mu$g ml^{-1}.

be possible and exploited for therapy. Figure 2 shows that, indeed, administering an *appropriate* dose of antigen directs our model immune system back to tolerance. This is the good news. The bad news is that the transition does not occur when the successful antigen dose is varied by less than 10%.

Figure 2 also indicates that the autoantibody concentration A_b remains in the stimulative range of the effective response function (shaded region in Fig. 1) during a substantial period of time. In fact, during the transition from the autoimmune to the tolerant state. This is a key feature of a successful transition from the autoimmune state back to the healthy one.

We have thus arrived at the discomforting result: whether or not A_b remains stimulative for A_c over an extended period of time depends critically on the amount of antigen V that has been injected. This sensitive dose-dependence raises the question: can we improve the therapeutic procedure and render it much less sensitive to the injected dose by administering antigen repeatedly?

3. Adaptive Control

Our goal is now to develop a scheme of repeated injections of antigen V such that the autoantibody titer A_b is lowered to and stabilized *within* its stimulative range for the anti-idiotype c. To realize this, we propose to monitor the autoantibody titer A_b and inject a *fixed* dose of antigen ΔV only if A_b exceeds a certain threshold Θ_A. Since the procedure is based on a *steady* adaptation according to the *current* state of the system, a great variety of combinations of injection threshold and antigen dose is successful.

Figure 3 shows two successful transitions from the autoimmune to the tolerant state which has been guided by the *adaptive control* schedule of antigen injections. Once every x-th day, where x is at our disposal, the autoantibody titer A_b is determined and, if the threshold criterion is met, i.e. $A_b > \Theta_A$, a dose ΔV is injected. The procedure first lowers A_b and then resets it approximately to its optimally stimulative value $\sqrt{\mathrm{HL}}$. In Fig. 3(a) we have $x = 1$, in Fig. 3(b) $x = 5$. The truly adaptive quantity is the interval between the injections, if any. Injections stop

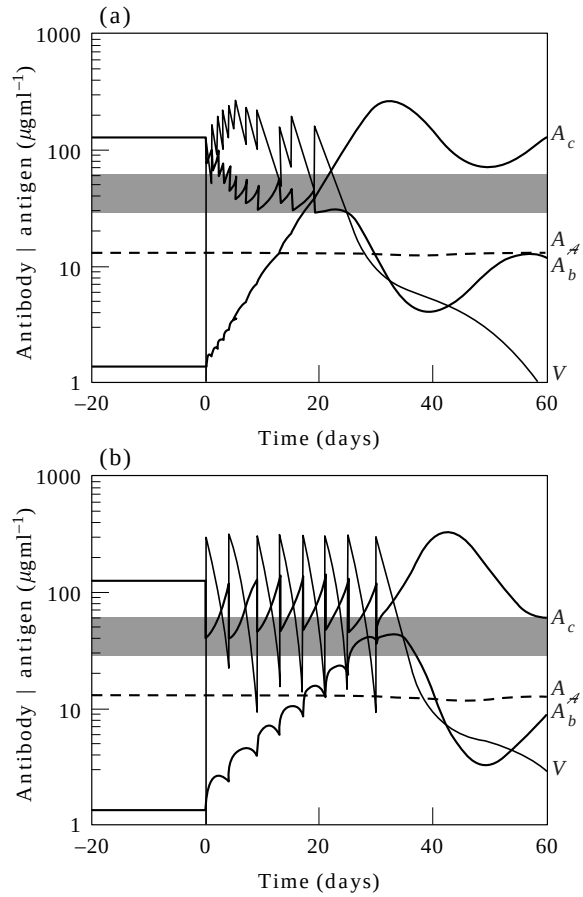

FIG. 3. Adaptive control. The antibody concentration A_b is measured every x-th day and, if it exceeds the threshold Θ_A, a fixed dose ΔV of antigen is added. In (a) $\Theta_A = 45\ \mu\mathrm{g\ ml^{-1}}$, $\Delta V = 120\ \mu\mathrm{g\ ml^{-1}}$ and $x = 1$ while in (b) $\Theta_A = 100\ \mu\mathrm{g\ ml^{-1}}$, $\Delta V = 300\ \mu\mathrm{g\ ml^{-1}}$, and $x = 5$. In (a), the first six injections of antigen (coupling to the autoantibodies) move A_b successively closer to the stimulative range, the shaded area in Fig. 1, which is reached on day 5. Five additional injections at intervals between 2 and 4 days suffice to keep A_b stimulative until, on day 19, A_c becomes larger than A_b. No further injection is necessary to attain the tolerant state. In fact, the crossover of A_c and A_b is a good indicator for when to stop antigen injections. One finds the labels A_c and A_b for the antibodies and autoantibodies (anti-idiotype and idiotype) on the right of the figure; in both figures the crossing corresponds to a downward motion for A_b and an upward motion for A_c. In (b) the first injection already renders A_b stimulative. Seven additional injections with 5 days separation reset A_b periodically. Both treatments result in tolerance, although the road to success appears to be somewhat "bumpier" and longer in case (b). The large threshold in (b) allows A_b to repeatedly approach H, where it becomes suppressive for clone c. The strategy is extremely robust with respect to both the antigen dose ΔV and the threshold Θ_A. When we use $\Theta_A = \sqrt{\mathrm{HL}} = 44.7\ \mu\mathrm{g\ ml^{-1}}$ as injection criterion, antigen doses $110 \leqslant \Delta V \leqslant 350\ \mu\mathrm{g\ ml^{-1}}$ are successful. For $\Theta_A = 65\ \mu\mathrm{g\ ml^{-1}}$ we have $102 \leqslant \Delta V \leqslant 397\ \mu\mathrm{g\ ml^{-1}}$, for $\Theta_A = 95\ \mu\mathrm{g\ ml^{-1}}$ we find $124 \leqslant \Delta V \leqslant 539\ \mu\mathrm{g\ ml^{-1}}$, and for $\Theta_A = 125\ \mu\mathrm{g\ ml^{-1}}$ we end up with the range $165 \leqslant \Delta V \leqslant 650\ \mu\mathrm{g\ ml^{-1}}$. Parameters are the same as in Fig. 2.

once the transition to the tolerant state has been completed. So the procedure is self-terminating. In practice, one could monitor the anti-antibody together with the autoantibody titer and stop the treatment once the former reliably exceeds the latter.

As desired, the anti-antibody concentration A_c increases steadily throughout the treatment due to its stimulation by A_b. Furthermore, the growth rate of A_c remains almost constant despite noticeable fluctuations of the value of A_b. This lack of sensitivity of the growth rate of clone c is an additional benefit of keeping its field h_c close to the optimally stimulative field at the maximum of the response function f^*. At its maximum f^* is approximately quadratic and small deviations from the optimal field lead to even smaller deviations from the optimal growth rate.

Our adaptive control strategy has two prerequisites. Since it aims at stimulating a *specific* anti-idiotype c so as to enable it to regain its dominance over the autoreactive clone b, the anti-idiotype still has to be present. As we have already noticed, in many instances it is. Furthermore, the clearance rate of the antigen has to be large enough. More specifically, it has to be larger than the growth rate of the anti-idiotype. Injecting antigen V can by itself only increase the field h_b of the autoreactive clone since $h_b = u_b + A_c + V$. We have to rely on sufficiently fast antigen clearance by the immune system so as to *de*crease the field h_b and, in so doing, keep b alive and, hence, stimulative for c.

4. Discussion

Although our model would allow us to calculate a near optimal injection schedule with varying doses ΔV, there is no hope for achieving a quantitatively reliable mathematical description of the immune network in the near future. What else, then, can we do? We have therefore proposed to fix the antigen dose and base the decision to actually inject antigen on the current autoantibody titer. Figure 3(a) is an example of a successful treatment where we inject the constant dose $\Delta V = 120\ \mu\mathrm{g\ ml^{-1}}$ provided A_b exceeds $\sqrt{\mathrm{HL}} = 45\ \mu\mathrm{g\ ml^{-1}}$.

The first six injections on days 0–5 reduce A_b successively until it reaches its stimulative range. Five additional injections (on days 7, 9, 13, 15, and 19) suffice to keep A_b stimulative the rest of the way. We would like to stress that we do not use a large first dose in this simulation. Although a well-chosen large first dose speeds up the adjustment of A_b into its stimulative range, as shown in Fig. 2, it is not necessary to complete the adjustment in a single step. Moreover, choosing too large an initial dose would jeopardize the success of the entire treatment in that it could suppress A_b too strongly and thus hinder it to stimulate clone c sufficiently.

Our strategy is adaptive in a very straightforward way. We periodically measure the autoantibody titer and, if it exceeds a certain threshold, we inject a fixed dose of antigen. Thus, the adaptive quantity is the interval between injections. The threshold is simply the square root of the product of the autoantibody (H) and the anti-antibody titer (L) before treatment. That is to say, $\Theta_A = \sqrt{\mathrm{HL}}$. The reason why becomes evident by returning to Fig. 1 and noticing that Θ_A is of the same order as h_{max}. Once the transition to the tolerant state is completed, the autoantibody titer remains below the threshold and renders our strategy self-terminating. Though not necessary, checking the anti-antibody titer occasionally helps to determine the end of the treatment. No further injections are needed once the autoantibody titer has fallen below the anti-antibody titer.

As is illustrated by Fig. 4, adaptive control is very robust. Antigen doses and thresholds differing by a factor of 4 are suited to achieve tolerance when the autoantibody titer is measured daily. More frequent measurements stretch the range of suitable antigen doses even further. This robustness with respect to the antigen dose promises that actual therapies may not require fine-tuning the antigen dose to fit the peculiarities of individual patients. In addition, a less frequent monitoring is required for the favorite laboratory animal, the mouse. Figure 3(b) illustrates that here the procedure works equally well, despite the large intervals.

We are confident that our results are also robust with respect to the underlying mathematical description. The strategy is founded upon two essentials. First, formation of antigen–antibody complexes reduces the autoantibody titer

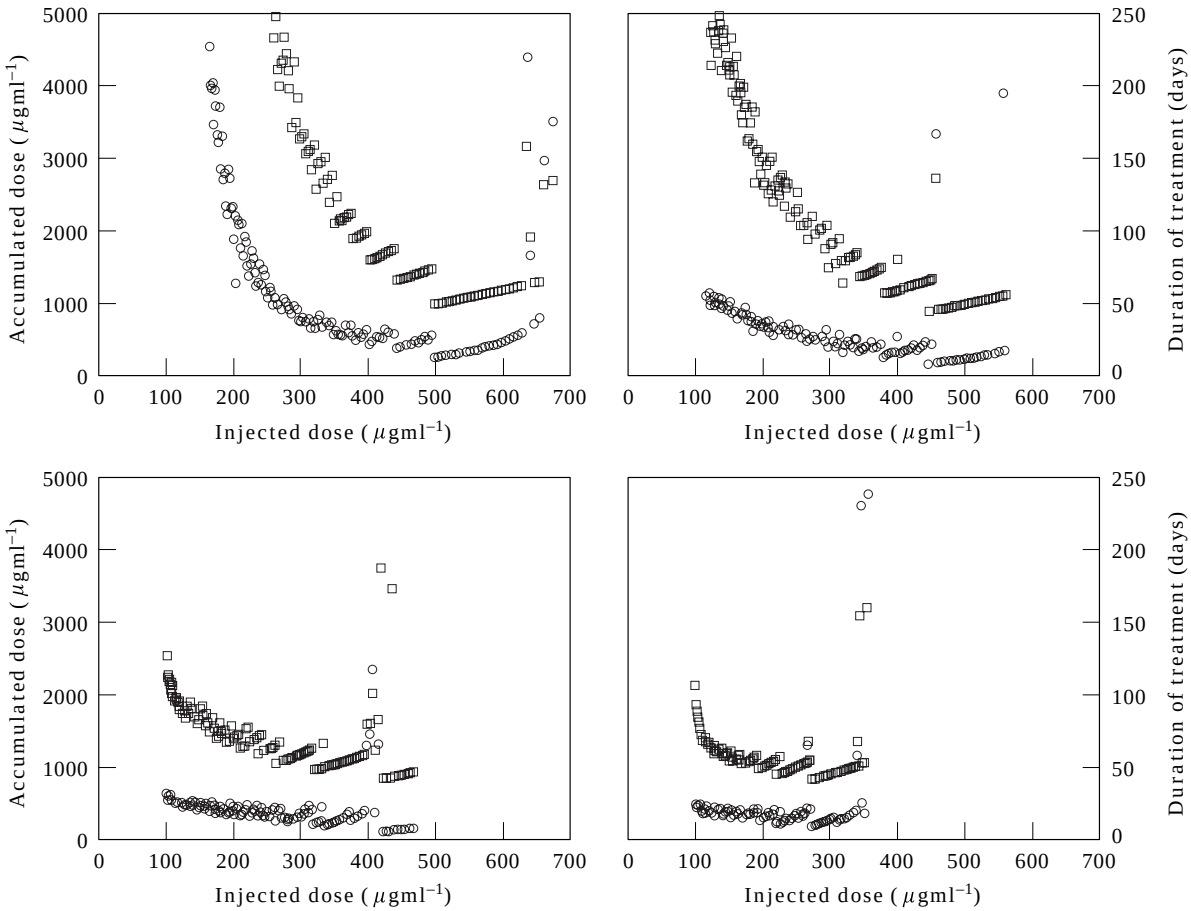

FIG. 4. Robustness of adaptive control. We show the accumulated antigen dose (○, scale on the left) and the duration of treatment (□, scale on the right) as a function of the injected dose for different injection thresholds $\Theta_A = 125$, 95, 65, and 45 μg ml^{-1}, left to right and top to bottom. For each injection threshold, the injected dose can be varied over a wide range (three to five-fold). The plots indicate that, in our model system, an injection threshold of $\Theta_A = 65$ μg ml^{-1} (about half the autoantibody titer) is optimal in allowing a successful treatment for injected doses ranging from 100 to 500 μg ml^{-1} where the treatment typically takes about 50 days. For Θ_A close to the autoantibody titer (125 μg ml^{-1}) the treatment takes slightly longer and requires a slightly higher total dose. However, the treatment can still be completed in less than 100 days for injected doses between 300 and 600 μg ml^{-1}. The system parameters are the same as in Fig. 2 and the autoantibody titer is measured every day.

quickly (on a time scale of hours). Second, the dichotomy of autoimmune and tolerant state, which is essential to our interpretation of idiotypically regulated B cell tolerance, requires that the dose-response relationship of a B lymphocyte is bell-shaped on a logarithmic scale, a well-established experimental fact (Celada, 1971, 1992; Dintzis *et al*., 1976, 1982; Vogelstein, 1982; Goldstein, 1988; Metzger, 1992). In fact, adaptive control exploits the bell shape to advantage whereas the scale might be any.

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