:I would like to understand the simplest possible model equations that can produce the range of dynamical behaviors that are biologically reasonable for a model of Th1-Th2 self-promotion and cross-inhibition. As such, I will explore several different models, all of which start from the basic structure.

**Model 1**

Here I am assuming there is some baseline T cell proliferation that is independent of the T-cell population itself. This could be driven by cytokines produced by other molecules. I use the Hill function to model self-promotion of T cell proliferation, and to model cross-inhibition by the other T cell population. Note that I am modeling cross-inhibition as a reduction in the proliferation rate, since this is more biologically reasonable than modeling it as a loss term in the equation. I also include a baseline loss rate of T cells.

To analyze this model, it is convenient to nondimensionalize it. In particular, I can nondimensionalize the T cell populations as and time as . With the dimensionless parameters (the baseline proliferation rate relative to the loss rate when the T cell population is at the abundance where proliferation is half its maximum value), (the maximum proliferation rate relative to the loss rate when the T cell population is at the abundance where proliferation is half its maximum value), (the ratio of the T cell abundance where cross-inhibition is half its minimum to the T cell abundance where self-promotion is half its maximum). This nondimensionalization makes parameter estimates clearer. In particular, it is clear that , so that self-promotion of proliferation is much stronger than baseline proliferation. It is also clear what choosing versus implies about the strength of self-promotion versus cross-inhibition; it seems likely that (self-promotion is stronger than cross-inhibition). This leads to the following model:

To determine whether multistability is possible in this system, it is good to work with the system’s isoclines. These are given by the solutions of this equation:

Notice that is not an isocline of this system because of the baseline proliferation term. In order for the isocline to exist in the positive quadrant, the numerator and denominator must either both be positive, or both negative. The denominator is positive for . This guarantees that the numerator will be positive as well (the numerator simplifies to at ).

Whether multistability is possible depends on the shapes of these isoclines. If the shapes are too simple (e.g., if they were straight lines), then there can only be a single intersection of the isoclines, and hence only a single equilibrium. To get a sense of these shapes we can look at the derivatives of this isocline with respect to the state variables.

The first derivative is always negative, meaning that the isoclines are decreasing functions. The second derivative is always positive, meaning that the curvature of the isocline doesn’t change. The isoclines will have a shape like the following:



With two isoclines that each have this shape, the number of possible intersections is small. In fact, if the parameters for each response are the same (e.g., , etc.), then there will only be a single intersection, and thus bistability will not be possible.

**Model 2**

The first modification that we can make to the simple model is to strengthen self-stimulation, for example in the following way:

The only change between model 1 and model 2 is the additional in front of the proliferation term. This changes the interpretation of the parameter . Whereas before, had units of T cells/time, here it has the units of 1/time.

Again, we can nondimensionalize the model. I can still nondimensionalize the T cell populations as and time as , but my dimensionless parameters are , , and Thus the comparison of and is not as direct as before, as the parameters have a different interpretation. The model is now

Nevertheless, we can again examine the isoclines:

Again we see that for the denominator to be positive, and that this will guarantee that the numerator is positive as well. This suggests that should be a small number.

The shape of the isocline can be assessed from the derivative:

If , then this slope is always positive. However, that doesn’t make a lot of sense since that would require for a positive value for the isocline. If then it is possible for the slope to be zero (i.e., for the isocline to change directions). This occurs when . This is actually important because such unimodality creates more opportunities for multistability, as two unimodal curves can intersect in as many as four points.

However, numerical simulation of a feasible set of parameters that produce multiple equilibria show that the multistability of the appropriate type (e.g., bistability of polarized equilibria) appears unlikely. Given this set of parameters , the isoclines, equilibria and vector field are shown below. Here there are three possible equilibria, two of which are unstable (open circles). The stable equilibrium represents a low co-expression equilibrium. If there is any initial polarization in the response, the system can end up in a dynamical regime where one response blows up to infinity. Essentially, the self-promotion loop overwhelms cross-inhibition.



By increasing the value of , you can increase the number of equilibria, but you still have only one that is stable, representing low co-expression and then a tendency for the system to explode towards an accelerating, unrestrained Th1 or Th2 response.



Having explored this model more, it is clear that can have 1, 3, or 5 equilibria. If the number of equilibria is 3 or 5, the low co-expression equilibrium will be stable, and all others will be unstable; if there is only a single equilibrium, it will be an unstable high co-expression equilibrium. Thus, the general behavior of this system is biologically implausible: runaway proliferation of either a Th1 or Th2 response.

**Model 3**

Here, I switch the self-promotion to a Hill function with an exponent of 2, which should promote a more switch-like behavior for the system. This exponent is supported by previous work suggests that cytokine-mediated self-promotion has a Hill exponent of two (both in Andy Yates’s work and in Ed’s paper). The model for the Th cell population becomes:

This model can be nondimensionalized identically to model 1, with the same interpretations of the parameters.

The isoclines are

Again, multistability is facilitated by having the slope of the isoclines change sign. Taking the derivative of the isocline with respect to :

The slope will change signs when the term in the parentheses in the numerator is zero, which depends only on the value of . In particular, the solutions of are only real if is small (in particular, it must be less than 0.2). Thus, if baseline stimulation is too large, the sign of the slope will be constant. However, if it is less than this value, there are multiple possible places where the slope can change sign (because the function is cubic).

For the parameter set , there is true multistability, with four stable equilibria, representing a stable low co-expression equilibrium, a stable high co-expression equilibrium, and two polarized immune response equilibria. It is useful to think what these parameter values imply, given the nondimensionalization we used: and . Thus this choice of parameters implies that self-promotion leads to T cell proliferation that is 20 times faster than baseline (i.e., ) and cross-inhibition is much weaker than self-promotion (because, e.g., the Th1­ cell abundance that causes self-promotion to be half its maximum is 10 times smaller than the Th1 cell abundance that causes cross-inhibition to be half its minimum). Thus we have both very strong self-promotion *and* very strong cross-inhibition.



If you weaken the baseline response (reducing from 0.12 to 0.08), you lose the high co-expression equilibrium, and end up with only three stable equilibria representing low co-expression or polarization. Weakening it further can lead to a situation where only the low co-expression equilibrium is stable.



Whereas if you strengthen the baseline immune response (increasing from 0.12 to 0.15), you end up with three equilibria representing polarization and high co-expression. Any further strengthening and the only stable equilibrium is high co-expression.



Manipulating other parameters can also change the behavior of the system. For example, strengthening cross-inhibition by reducing the value of from 10 to 6 has a similar effect as weakening the baseline response: the high co-expression equilibrium is lost.



Weakening cross-inhibition by reducing the value of from 10 to 15 increases the basin of attraction for the high co-expression equilibrium, making that outcome more likely.



Strengthening self-promotion (increasing from 2 to 2.5) also causes the loss of the low co-expression equilibrium:



If you increase it much beyond this point, the only stable equilibrium is a high co-expression equilibrium. Weakening self-promotion has the same effect as weakening baseline proliferation: first the loss of the high co-expression equilibrium, then the loss of the polarized equilibria.



In short, this model is *very* promising.

**Model 4**

The last model to explore is one that looks at stronger cross-inhibition, so I considered this model:

This can be nondimensionalized in a similar way as all of the other models, leading to

Again, we can examine the isoclines

If , the both the numerator and the denominator are positive, implying that the isocline will exist in the positive quadrant. The slope of this isocline is given by

While is expression is complicated, it’s clear that it must negative for all . Without explicitly into the second derivative, it is also quite complicated (a degree five polynomial) and thus there is the possibility for the second derivative to change signs, making the shape complex enough to allow multiple possible intersections.

With this set of parameter values , you do get bistability between polarized outcomes, but no possibility for any co-expression states at all. This makes intuitive sense: with very strong cross-inhibition, as we have here, any initial bias in the Th response will drive the system towards a polarized response.



If you weaken cross-inhibition by increasing the value of from 1 to 3, then the only possible equilibrium is a stable high co-expression equilibrium.



Given the shape of the isoclines, 1 or 3 intersections are the only possibilities, so this model will only have as possibilities a stable high co-expression equilibrium, or bistability between polarized equilibria.

Of course, more complicated models would also likely work, for example this one, but I doubt that it would produce any truly new biological phenomena.

The next issue is how to integrate this Th system with the immune-parasite system. The immune-parasite model we were using to demonstrate bistability was the following:

This is obviously quite simple and assumes that T cell proliferation is dependent only on the abundance of parasites, and has a loss term as if parasites were actually removing T cells, rather than suppressing T cell proliferation. The simplest way to integrate parasites into the T cell model above (using model 3 as an example) is something like the following:

Where the functions and are the parasites contribution to T cell proliferation. This could be a simple linear function, or a saturating function, whichever makes more sense.

One question to address is whether the simple immune-parasite model should have an amended form that makes the immune dynamics of that model a bit closer to the form of the T cell model (e.g., making T cell proliferation dependent on T cell abundance as well as parasite abundance, having parasite manipulation come in the form of a reduction in proliferation rate rather than a loss term).