**Notes on papers:**

**Shudo & Iwasa 2001**:

Model of investment in constitutive and inducible defense. Model assumed exponential parasite growth in absence of immune response. Investment in constitutive defense measured by single variable *z* and investment in inducible defense measured by variable *x*. Found optimal *z* and *x* to minimize cost to host, where cost was a sum of constitutive + inducible defense costs and cost of parasitism. Parasite abundance modeled as:

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| --- | --- | --- |
|  |  |  |

And the cost is modeled as

|  |  |  |
| --- | --- | --- |
|  |  |  |

Inducible defense only kicks on after some lag *L*. The total cost depends on the investment in each defense, the probability of infection *p*, and the cost of parasitism, which is just the cumulative parasite population over the duration of infection times the cost per parasite *K*.

What the authors find is that, over much of parameter space, constitutive defense alone is favored. Otherwise, joint investment is likely, with inducible-only defense common only in extreme circumstances. Quoting from the article itself: “the constitutive defense is more heavily adopted when it is more effective and less expensive, the initial abundance of pathogen is large, pathogen growth rate is high, difference in time delay is large, pathogen damage is severe, and pathogen attacks more frequent. Adopting both defenses is optimal if the pathogen causes a great damage (large pathogen dose, high growth rate, and severe damage, and pathogen attack is likely) and if inducible defense is more cost-effective than constitutive defense (e0/c0 < e1/c1).

There are a number of limitations of this study, however, the most important of which is the fact that it is focused on the optimal investment for a single host, without any consideration of population-level consequences. In particular, the probability of infection is the result of disease dynamics that will themselves be affected by each host’s investment in defense. Thus, in reality, *p* should be a function of *z* and *x*, and that would affect the evolutionarily stable investment (as opposed to the optimal investment).

Additionally, the lack of a dynamic immune response is problematic, as both the resource and IP costs to the host of mounting an immune response probably depend on both the magnitude and duration of the response. This is a more minor concern, as here the duration of the response is determined by the duration of parasite presence, which is inversely proportional to the investment in defense – so a larger response leads to a shorter infection and thus a smaller parasite-induced cost, but a larger cost to the host. However, this may underestimate the cost to the host compared a response that takes the actual abundance of immune effectors into consideration: here a large investment leads to a short infection, but in reality a large investment in immune proliferation may lead to an over-reaction that causes additional self-harm as the immune cells are still around long after the parasite population has been eradicated. Definitely a second-order concern.

At a more mundane level, the implementation of both immune response and cost is overly simplistic.

**Frank 2002**

“Evolution of a pulsed character”

Here Frank is thinking about immune responses as an example of a pulsed response and exploring how evolution shapes a pulsed, dynamically regulated reponse. He points out 4 difficulties:

1. The functional character is a time-varying rise and fall of a factor, such as killer cells that can fight an infection. The dynamical path of killer cell abundance is shaped by the benefits of defense and the costs of host resources or IP. Such paths are a more complex notion of a “character” than static, “parametric” traits.

2. Component parts of the response have their own dynamics and can be measured as separate characters. For example, immune cells are stimulated to divide by an increase in the concentration of some other molecule that is secreted by cells that recognize invaders.

3. Analysis requires dynamic optimization, a more complicated set of mathematical techniques.

4. Optimization shows the direction of natural selection on the value of the variatbles that govern the dynamical response. The next step is to analyze the strength of selection on each component in order to understand which characteristics of populations are likely to be variable and which are likely to be nearly constant.

The model has three variables: *X* is the conc. Of the molecule that increases directly in response to parasites, *I* is the concentration of immune cells that can kill the parasite, and *P* is the concentration of parasites within the host. The dynamics are given by

Thus the molecule is always around, always being produced at a density-independent rate *a*. Whenever the parasite shows up, new immune cells are produced at a rate that depends on the abundance of parasites, akin to a predator functional response. When parasites are super-abundance (*P/*(*k* + *P*) = 1) and the increase in abundance of *X* is exponential ((b+d)X-dX=bX). There is also a density-dependent bit, from the bKX^2 term, which sets an upper bound on the abundance of *X*. The number of immune cells increases following a very similar function. Finally, the parasite grows in a density-dependent manner in the absence of immune cells, but decreases according to a Type II functional response. Interestingly, the abundance of *X*, *I*, and *P* are all capped at 1/*K.*

To determine fitness, the system is initialized at the parasite-free equilibrium. This equilibrium is approximately of order , then 1 parasite is introduced the system is integrated forward until *T*=50. Fitness of the host is given by

where is the baseline level of immune cells in the absence of parasites. Thus the higher the standing level of immune cells (constitutive cost, determined by alpha/delta), the lower the baseline level of fitness, and fitness is further reduced by the induction of the immune response (the amount of time that I > I\*) and by the total abundance of parasites.

The host controls its response through *a, b, d, alpha, beta, and delta*. Frank is going to consider the evolution of these variables in response to changes in the other parameters, in particular the immune response half-saturation constant *v*, the fitness cost for constitutive defense *c*, the fitness cost for induced defense *sigma*, and the fitness cost for parasites *gamma.* He uses a genetic algorithm approach to find the optimum control parameters in response to changes in these varied parameters.

Once the optimum was found, he set all variables at their optimum and then varied one variable until he found values above and below the optimum that caused a 10% decline in fitness. This, he treats as a meaure of the strength of natural selection, with short distances between the optimum and +/- 10% indicating strong selection.

Results:

Response of *a* (sets the baseline level of recognition molecule):

* increasing the half-saturation constant of the immune killing function *v* has essentially no effect on *a*
* increasing the cost of parasitism *gamma* has essentially no effect on *a*
* increasing the cost of the induced response *sigma* weakly reduces *a*
* increasing the cost of parasitism does change the fitness landscape, with strong selection when *gamma*  is larger.

Response of *b* and *d* (replication rate and decay rate of recognition molecule in the presence of the parasite

* almost always fixed at the maximum possible level
* fitness landscape is relatively flat, so selection may permit a lot of variability in this variable

Response of *alpha* (sets constitutive defense level)

* increasing *v* (making the immune killing function less sensitive) weakly increases *alpha*
* reducing the cost of constitutive defense weakly increases *alpha*
* increasing the cost of induced defense sharply increases *alpha*
* fitness landscape responds primarily to the cost of induced defense – no variability at high *sigma*

Response of *beta* (induced response proliferation rate)

* again, primary response is to increasing the cost of induced defense *sigma*: increasing this cost sharply decreases *beta* and fitness landscape becomes sharper

Reponse of *delta* (induced response decay rate)

* fixed at very high levels

Take-away message: again, as in Shudo & Iwasa, we see a privileging of constitutive over induced defense. The cost of induced defense is the most important driver of the optimal values of all of the other control parameters. A high premium is put on rapid decay of response, which is a trivial and obvious result, as is the fact that the signaling molecule should build up quickly.

Basically, I don’t get much out of this paper. It showed a bunch of intuitive things and no non-intuitive things. Probably not worth citing.

**Hamilton et al. 2008**

Also looked at optimal investment into constitutive vs induced defense, but this paper was more interesting in that it actually looked at how variation in the parasite influenced this investment. This is much more in line with other studies of phenotypic plasticity, which had shown that plasticity will evolve only in response to variability: if the environment is static, there is some fixed trait response that will optimize fitness in that environment, and plasticity is unnecessary. Their model is also focused only on the optimization of individual fitness with no conception of how investment might depend on the dynamics of the environment (this appears to be a really big gap in the literature).

The model they consider is quite simple:

where *P* is the number of parasites and *R* is the size of the induced response. The constitutive response is simply given by *k*, and is a fixed quantity. Again, the constitutive and induced responses combine additively. From the perspective of the parasite, the induced response behaves like a predator with a type I functional response. Interestingly, the *stimulation* of the induced response does not depend on the size of the response, but only on the number of parasites, whereas the *decay* depends only on the size of the response, and not on the number of parasites. **Note: our macroparasite energy budget model has this same feature. Stimulation depends on reserve biomass and parasite biomass, but decay depends on biomass of the induced response.** This guarantees that the induced response always returns to 0 once the parasite has been cleared. The model has a coexistence equilibrium of

so the induced response equilibrium depends on the parasite’s growth rate , the attack rate of the immune response , and the investment in constitutive defense , and the parasite’s equilibrium depends on , the stimulation rate of the immune response and the decay rate of the immune response .

If the dynamics of the induced response were instead *aRP—bR*, the equilibria would be different:

In other words, the parasite’s equilibrium abundance would be independent of the induced response. Or, more aptly put, the equilibrium abundance of the parasite would not depend in any way on parasite traits, but only on the efficacy of the induced response. In that sense, the results suggest that the first model is more biologically intuitive, even though the derivation seems less biologically intuitive.

Anyway, I digress. It turns out that the coexistence equilibrium of the system is unstable (unsurprisingly) with long period cycles. To deal with that case, they assume that if the parasite abundance falls below some threshold that the parasite goes extinct. Thus, the immune response can clear the infection.

The authors assume that the cost to the host at any point in time depends on (1) the size of the parasite population; (2) the size of the induced response; (3) the size of the constitutive response (*k*):

They also assume that , which seems a bit weird, on the face of it, but I suppose is not all that weird since it is probably only the relative costs that matter. The total cost to the host, therefore, is

The goal of the analysis is to find values of *a* (the proliferation rate of the induced response) and *k* (the investment in constitutive response) that minimize.

(An aside: This is a little weird because of the difference in scale between and . *gRP* is the total parasite mortality due to induced response and *gkP* is the total mortality due to constitutive response. The units of [*g*]=1/(immune cells \* time), and the units of [*k*]=(immune cells). The units of *a*, however, are [*a*]=(immune cells)/(parasite \* time). Thus and are not on the same scale, and are thus somewhat hard to compare.)

The results are pretty straightforward: if the host encounters only a single type of parasite (specified by *r*), then the optimal strategy is to choose an appropriate level of *k* such that the parasite cannot persist (*k* just slightly greater than *r/g*). If the host encounters a distribution of parasite types, then the total cost is the weighted average over the distribution, and the optimal strategy is to invest more in induced defense as well. In particular, echoing the results of Shudo & Iwasa (2001), if the parasite is not too dangerous (mean *r* over the distribution is small), then only induced defenses can be the optimal strategy. Otherwise, investment in both induced and constitutive defenses are optimal. Similarly, as the fraction of time the host is parasitized increases, so does the investment in constitutive over induced defenses (for any given distribution of parasite types). This also agrees with Shudo & Iwasa.

Big picture take-away: This study, in echoing the results of Shudo & Iwasa, suffers from the same weaknesses, in particular that the fraction of time parasitized is an important determinant of investment, but one that depends on the investment strategy through the feedback on population dynamics. This paper also suggests that coevolutionary dynamics will be really important in driving investment in defense (through the fact that parasite variability matters). So, two big questions that one could immediately imagine tackling are: (1) how does epidemiological dynamics affect the investment in constitutive versus induced defenses; (2) how does coevolution affect this investment?

**Tate and Graham 2015**

Develop a model of resource allocation to development, immunity, and infection within growing larval insects attacked by parasites that specialize on different developmental stages. The key challenge in constructing such a model, and the biological process that the authors were interested in, was developmental interference. DI encompasses several different mechanisms by which an organism’s current developmental state can negatively impact its ability to mount an immune response. For example, young larvae cannot rapidly deploy hemocytes because hematopoietic organ maturation requires several instars to complete; another example is that moulting depletes PO, increasing susceptibility immediately following moulting. Thus, DI might alter optimal investment in immunity. Moreover, parasites, by depleting energy, might further complicate matters by making it more difficult to develop or mount an immune response, exacerbating any developmental interference.

The model they derive is

The parameter is actually a function of developmental stage, reflecting the fact that the total energy mobilized should depend on how close the animal is to completing its development:

is this equation is also a function dependent on the state of the immune system, in particular,

depends on infection status. If , (where ). If , .

is also a function that allows immunity to take priority over development when , so

where quantifies the magnitude of DI (between 0 and 1).

This is a really neat model; I very much like the biological intuition underlying its derivation. It does have some behavior that is potentially problematic (I think).

Imagine an organism that has completed development (so ), and has just successfully repelled a parasite (so but because of immune depletion during the repulsion). Then because development is done, because , , , . The amount of reserve that is mobilized is

The amount of mobilized reserves going to immunity is

The amount of mobilized reserves going to development is

Note that this implies that there is energy going to development even though , which means that some amount of mobilized energy is simply lost from the system, meaning that the system is not closed. This may not matter too much for the results, but it is worth keeping in mind as we develop our own model.

I have a similar concern regarding the parasite’s dynamics; when , the parasite steals a large chunk of mobilized energy, but most of it is not used by the parasite for any purpose.