

[SQUEAKING]

[RUSTLING]

[CLICKING]

HAZHIR

The predator-prey model, if you have looked at the classical model or have even heard of it before, you associate

RAHMANDAD:

it with oscillation. It's kind of the primary mode that the Lotka-Volterra has introduced in the literature. It's interesting because the oscillations are motivated by real phenomenon. So there were kind of fish populations that oscillated, hare and lynx populations that oscillate.

So this provided a theory for these oscillations that was plausible and made sense. But when you look at the actual model, it doesn't have the saturation effect. That is basically each predator is consuming a fraction of the prey every period of time.

And that's very weird. You can't consume a fraction of the prey. You can consume a number of prey, and that makes a big difference. So that's the mechanism that was missing in the classical one that we discussed how to approach it and model it last time. And basically, those saturation effects create some additional non-linearity, although the original model is non-linear, but it kind of creates a more subtle non-linearity.

Now, when you add those saturation effects, basically, the model is much less likely to oscillate. In fact, you have to make some strange formulations, and very narrow parameter ranges create oscillations. So the predator-prey story of oscillations actually is not quite right in a way, which opens up the question of, OK, what creates those oscillations in the real world?

So the mode of behavior that comes out of the more realistic predator-prey model, and it is not the model that is - we are not the first ones creating it here in this class, of course. There are kind of lots mathematical, biology work that has built those saturation effects into it. Many of them use the formulations you had, which was $1/(1 + ax)$ that we tried.

There are names even for these formulations, the first order saturation effect. And then they have a second order saturation effect. and so on.

So those don't usually oscillate. They usually end up with overshoot and collapse or overshoot and equilibrium type of dynamics. And then the real-world oscillations in these systems, perhaps, are coming from other mechanisms that are not captured in a simple predator-prey model.

Most likely, there are a movement of populations inside geographic regions. That is, you deplete some part of the population in a neighborhood. And then from other Neighborhoods, gradually, populations of prey come in, and the predators in the central area leave. And that might be the more likely source of oscillations in the real world.

So that's one set of more connecting with the empirics in this case. The other thing is that when you add these saturation effects, we didn't really go through the equilibrium conditions last time. But putting the model into equilibrium becomes harder. So some of you tried to put it in equilibrium. It is fairly straightforward with the classical formulation.

But with these more non-linear saturation effects, you have to write the equations and see if you can find it. You may end up choosing a saturation function that is more solvable analytically, which is another common approach. But anyway, that becomes a hard problem. So that's another thing to keep in mind with this class of models.

The last item is that something we didn't discuss, but it is very common in the biologically motivated models, is that in outflow from the prey, which is the hunting, directly becomes the inflow into the stock of the predator, with a fractional conversion rate. That is basically conservation of biomass. You eat animals that turns to the bodyweight of other animals, which reduces one degree of freedom from the model.

So your growth rate for the predator is not completely independent parameter that you can play with while keeping everything else in place. It actually would get-- and that is the main feedback rather than the death rate of the predator in the typical models for how the feedback of the predator availability impacts the growth rate of the predator.

So you look at the classical model, that's how it is formulated, but also all of those more advanced or more complex models that have these saturations still make this assumption. So those are just a few reflections on the predator-prey model.

With that, let's get started talking about our model for today, which is the pharma or drug pipeline model. And let's get started with your reflections and things that you found to be challenging that are helpful to probably attend to a little bit more as we discuss. So thoughts here and online.

AUDIENCE: When I added the failure rates, I couldn't account for adjustment in the stock so that everything stays at equilibrium. And I'm sure that my model is wrong.

HAZHIR Equilibrium with failure rates and adjustment for stocks. These are very important formulations that we definitely
RAHMANDAD: want to discuss today. Other challenges, [INAUDIBLE].

AUDIENCE: I have issues approaching the controller side, but the decision-making that goes into how the timing to-- the supply chain of itself was a lot more tangible than [INAUDIBLE].

HAZHIR So start rate for drugs as a function of what you want to achieve. Is that the core formulation? So this is probably
RAHMANDAD: the most important formulation. Ultimately, the rest of this model is basically physics.

The real decision is the start rate of new drugs to drive the desired revenue ultimately. So that's absolutely the heart of the model. We should definitely dig deeper into it. Very good. Other challenges, other issues?

So these are good. I thought maybe I share with you when I enter looking at any of these models, what are the things in my mind that I'm looking for so that it kind of gives you a little bit of a lens to more generally critique, think about models.

So there are basics like the units non-negativity of physical stocks keeping those in mind. So that's for every model applies I think, very straightforward. And we are building those habits of looking at those basics. I'm seeing that the models you're submitting are usually unit OK, which is great. Thank you.

Then the stock adjustment, that is, how do you adjust what is in the stock? And Ali mentioned that is a non-trivial formulation for this one. So generally, you need a desired level, and you need to compare that with the current level and make an adjustment.

But what is the desired level here? When you have two factors that are making it complex, one is the failure rate, the other is the possibility of the growth. So for a system that is in a steady state, it is relatively straightforward to put together a desired level for a system that you want it to be also growing. What is the desired level that allows it to grow at the rate that you want it to grow?

And then the same two considerations come into the replacement question. That is, now we have these drugs basically becoming obsolete or going out of patent. And therefore, they wouldn't be contributing much to your revenue. So how do you replace to account for the significant delays in the pipeline process that then interact with the growth rates you want?

So if I want to grow 5% a year and I'm retiring 10 drugs today, what I'm entering on the other side will become a new drug years from now. So I need to actually account for a lot more that need to go into the process to get the growth rates that I want. Otherwise, just replacing what goes out will not do the trick.

And then I'll think about equilibrium. And this is one of those models that you definitely need to put it into equilibrium. Otherwise, so many things will happen inside the model, you can't trace what is happening. So for good analysis, having equilibrium is key.

So that's the key things I'm looking for. And I think we already have talked about the idea of the model last week. So I think everybody here knows what the basic problem definition was. Any thoughts while I'm opening the models that have been submitted so that we can take a look.

AUDIENCE: We'll probably get into this. But my guess is the standard stock management formulation, which has first order negative feedback controls for comparing desired level to actual isn't enough to hit desired [INAUDIBLE] when there's a growth.

HAZHIR That's right. That's right. It's not enough. So the simple equilibrium one is relatively simple. You just need to
RAHMANDAD: account for failure rates. Otherwise, it's kind of the standard formulation you already know. So the real challenge, in my view, at least coming into this, was how can you incorporate the growth trajectories. Now we'll see what are the other challenging things that may surface as we look at the model.

So first the basics. We have the three phases of drugs in different phases and then of clinical trials and then drugs in the market. So the basic physics are all there. We have failure rates to nowhere. And then we have the time for going out of patent.

And in this case, basically for drugs, they lose 90%, 95% of their revenue once they're out of patent the same day basically because generics are introduced in the market right away. People know what date the patents are expiring, and they bring generics the same day that are much cheaper, and everybody switches to those. So that's good.

Then we have the basic flows for every stage. So the drug finishing phase 1 is the number of drugs in phase 1 divided by average phase 1 trial time. Drugs finishing phase 2 similarly, phase 3 similarly.

And then that is divided between drugs that go to nowhere versus drugs that go to the next phase based on these success rates for each phase. So that's all good. And this model is under development. So I think I opened the version of the model that was extended but not finished.

So this is pretty standard. I think most of you probably were using similar ideas here. So that's good, those basics. Then let's look at what is happening with the desired drugs. So you have the desired revenue here. That's kind of driving the system. And the way Alban has formulated it it's some initial multiplied by some input. That's a good formulation.

So then you can change those inputs. And I think view 2 may have the inputs. Yes. So you can have a step. You can have a ramp. You can have exponential growth. You can have sinusoid. So this is a good formulation to get whatever input you want into your desired revenue. And then desired revenue divided by annual revenue per drug gives you the desired drugs in the market. So that's also good.

You also calculate current revenue using that. So this is desired drugs in the market, which is correct. So that's what you look at. You can then initialize your drugs in the market using that. That's a good formulation. So drugs in market will be initialized by the desired value.

And then you adjust. You look at the difference between the two to get the market adjustment from drugs in the market. That makes sense. This is the gap between the two divided by the time to adjust drugs in the market. So all of that is good.

You have similar ideas downstream. So let's take a look at them. So right now, the formulation that we have here is saying how many drugs go out of patents, and then that with some delay, some kind of perception delay leads to your replacement rate of sorts.

That is expected drug out of patent that adds up with the stock adjustment. So it is a replacement process stock adjustment, the classical formulation. Now what is problematic with this formulation? What doesn't it capture?

AUDIENCE: [INAUDIBLE] if you have a desired growth pattern.

HAZHIR So it is not accounting for the desired growth pattern. That's definitely the case. Then there is something else
RAHMANDAD: that is a little bit more subtle. And that is if you want to replace 10 drugs that are expiring and your success rate over the whole pipeline is only 10%, how many drugs do you need to start? 100 per year or month or whatever is the unit. It's years here.

That is not right now accounted for in this expected drug out-of-patent flow. So without accounting for that, this model will not do well. It cannot be put into equilibrium. It wouldn't generate what you need.

Now I might be missing something down the road in the formulation. Because there is-- as you can see in Alban's model, there is this kind of a cascade that you have a desired three to market, which is, I think, the flow here. And that flow, you want it to be in equilibrium at least, the same as expected drug out of patent.

AUDIENCE: [INAUDIBLE] just on your [INAUDIBLE]

HAZHIR Yes, so that's what I'm saying that maybe he's capturing it through that process. We wouldn't know that without
RAHMANDAD: simulating or asking Alban to explain. So Alban, if you are hearing us, you can unmute and tell us what the idea here is.

AUDIENCE: Yeah, I'm trying to capture the success rate through that desire straight to market that is trying to balance the outflow and the stock management. And then that informed the desire drug in phase III, the stock, accounting for the success rate. But not everything [INAUDIBLE] will become straight to market. And so I can build the stuff more than--

HAZHIR Yeah, so basically, because when you go into the desired drugs in phase 3, you are accounting for the success rate of phase 3. So you are dividing this-- so desired 3 to market, multiply it by average phase 3 trial divided by average phase 3 success rate would expand the number of desired drugs in phase 3.

So this is a good formulation for the desired phase 3. So this is a good practice. The only part that I'm wondering about is-- yeah, this should do fine. In equilibrium at least without growth and in equilibrium, you have the three to market adjustment. This would be zero because in equilibrium, this should be zero.

So the desire to market is basically the out of patent rate, which would be the same as three to market rate. So this is the flow that should come out of this stock. And if you have that flow coming out of the stock set, you can calculate the desire to stock based on that flow.

So this is a good formulation for the case that you don't have exponential growth. This works fine. And then the adjustment in the drug, you don't need to worry about it too much because it is in equilibrium zero. So it doesn't add to this desire thing.

Now, this formulation does something that is a little bit more subtle. And this one is not-- there is no single right answer. But let's think about two ways of formulating this adjustment. So one way is to get the desired drug in phase 3 from the expected drug out of patent or from this expected three to market without accounting for the adjustment for drugs in market.

So if you are making a big adjustment in the drugs in the market, I'm not going to change drugs in phase 3 based on the adjustment of the market-- the desired in phase 3 based on the adjustment of the stock of drugs in the market.

So if I'm missing a lot of drugs in the market, in the steady state, in the long term, I don't want to change my desired drugs in phase 3 that much. I want my desired drugs in the phase 3 to just flow based on what my total output I want it to be, total drugs in the market and out of patent I want them to be. So that's one way of doing it.

The other is what Alban is doing here, which is you say, no, actually, I want to more aggressively adjust all of the intermediate stocks up or down based on the gaps in my desired stock as well.

This is one of those things that I don't think there is a very clear best answer. Most of them have pros and cons. My preference is probably not to include this mechanism because it is harder to track what is happening when you have big gaps. But this is not wrong technically. Cathy, you had a question.

AUDIENCE: Yeah, I was just wondering conceptually when you're adjusting for these intermediary stocks, you can't control directly the start rate into phase 3. It's like filtering through. So the way I approached it was to accumulate the entire supply line and then only adjust based on as if all three stocks in the supply line were--

HAZHIR So tell us why you cannot do what you want to do. This kind of--

RAHMANDAD:

AUDIENCE: Or you can't do it directly. I can't start a drug from nothing and put it into phase 3. I have to go through phases 1 and 2 first. And so I suppose, yeah, in a deterministic model, you know how many you're going to get to phase 3 anyways. So I guess you can't directly control it in that sense, but I guess-- yeah.

HAZHIR So let's put this stochasticity aside. I think the stochasticity matters in this context, a lot because we are talking
RAHMANDAD: about a small numbers, but in expectation, actually, it doesn't make a big difference. That is, the expectations are fine, the deterministic model. So adding a stochasticity doesn't really make a big difference.

Here this cascade method actually is perhaps the only way to put this model into equilibrium in a way that works well. That is, you start with whatever is the desired final stock. Based on that, you calculate what is the inflow into that stock that you want it to be.

Based on that, you calculate the drugs in the phase 3 that gives you that inflow to the drugs in the market and then move backwards like that. So that is actually the way to put this model in equilibrium. So this is well done on that front.

The part that is more debatable is whether to include this third market adjustment in the desired three to market number that we have here or to do it in a different way. Now, there is another wrinkle here, and that is whether you get it out of expected drugs out of patent because this is just replacement.

Or you get it from your desired annual revenue, which then drives how many you want to get the drugs out of patent at that point in time. So that is actually a more important consideration for doing the equilibrium. And that goes to the issue of growth. I think this model wouldn't handle the exponential growth phase the way it needs to. But I think for the equilibrium case, it does well.

So I assume the rest of it is fairly straightforward, that is, replication of the same idea. So the desired drugs in phase 3 now lead to an adjustment for drugs in phase 3, so from 2 to 3. And that plus how many drugs are finishing phase 3 leads to the desire 2 to 3.

So this is, again, well captured. And the only kind of wrinkle is whether you include this adjustment in desire two to three or not when you want to calculate the desired levels for the previous phase.

If you don't, then you add up all of these adjustments for stocks as a separate adjustment for a stock variable. And then the desired phase 1 start rate comes partly from this previous adjustments and partly from the total replacement rate.

OK, good. So this is capturing several of the things that we want very well. Let's go with yet other model. Let's see. What is this one? So this is [? Hassam's. ?]

AUDIENCE: Mine, yeah.

HAZHIR OK, so--

RAHMANDAD:

AUDIENCE: I looked at the pipeline different. So you know about this perspective. But in this model, I'm thinking that drugs that start in phase I and finish phase I don't necessarily get [INAUDIBLE]

They sit in another stock waiting as potential candidates [INAUDIBLE]. And the same goes for phase II and phase III. And in reality, there can be multiple phase II drugs trials started in phase I.

HAZHIR But you have-- let me see, in terms of the phases, you have early-- oh, you have three phases. So where do they
RAHMANDAD: sit?

AUDIENCE: Repeats for the three--

HAZHIR I know, I know, so first of all, this is, formulation-wise, a more compact way of what we saw in Alban's structure.

RAHMANDAD: So drugs in trial are all subscripted, I assume, based on phase. Phase has phase I, phase II, phase III.

So this saves the space. This is nice and clean. I like it.

For our purpose, you could do this way or the way Alban did. Doesn't make a big difference. If you are doing it in practice for a larger model, this saves you some time in making the formulation. So that part is fine.

Now, there is the more conceptual point that [? Hassam ?] is making, that drugs don't necessarily continue to the next phase even if they don't fail. That is, you may succeed in a phase II but decide that, eh, this is not high enough in my priority list in terms of the promise of this drug that you keep it on a warmer. It's maybe, two years from now, there is a new technology, new indication, something changes that I decide to use, push this forward or not.

So that's conceptually right. In the level that we are modeling, it is not as critical because you can always say those drugs either will be continued or will be disposed of. So their pathway is one of these two. And you can incorporate that extra delay in the total phase ex delay that you have.

So as such, fine conceptually, but for this model, it can do the trick accounting for that. And the fact that we are using first-order delays makes a lot of assumption of a lot of heterogeneity between drugs. That is, if you're in this phase, anyway, you are going to be kind going through a lot of variance.

AUDIENCE: So the second conceptual difference is that you can have multiple phase II trials on the same phase I [INAUDIBLE] tasks, which is actually what happens out there.

HAZHIR So this is what you are doing in this model or not?

RAHMANDAD:

AUDIENCE: So if here we have a [INAUDIBLE], we have the three different investments in three different phases. So one can put more money on phase III, initiating more phase III on the candidates they have, or initiating more phase II on the candidates they have of phase II for initiating more phase I. So it's not just one lever of starting down the line, but three levels.

HAZHIR OK, so that is a more complex formulation.

RAHMANDAD:

AUDIENCE: We will get to the bad news or something [INAUDIBLE], the stuff that I'm happy I did. But then what happens at the end is that it becomes too complex. So I then put a lot of effort. So the decision-making part is not [INAUDIBLE].

HAZHIR OK, so this is an interesting-- again, for going with phase II out of a candidate in phase I, you have different pathways. You could actually target it for different conditions. You could target even different ways of administering drug for the same condition.

So there are possibilities that open up that is not a single one. And in the typical conceptualization, we don't make that distinction. [? Hassam ?] has done his PhD partly on this. So that's why he has the content domain knowledge that makes his model more complex on this front.

And that's fine. That's good. But it also makes it harder to do the rest of the things that--

AUDIENCE: So the connection between the phases is that if a company starts making-- starts more phase II, then they're using the novelty of the ideas that they've already passed in phase I, so the nonlinear relationship that is consuming up their phase I.

HAZHIR OK, so let me look at the equation here. So phase drugs in any phase are increased with initiating trials and reduced by failing trials or passing trials. So that's fairly straightforward.

AUDIENCE: The ones which are in trial. And then there's the ones that have passed.

HAZHIR Yes. And then drugs that have passed trials also have their own phases. So you may go into-- I have passed phase II, and I'm sitting there.

AUDIENCE: Yeah, it won't go obsolete after one.

HAZHIR Yes, so if something passes phase III, that is the one that makes money. So this becomes the-- revenue generating is the phase III one multiplied by revenues on the market. Got it. But then the start rate for initiating trials, you have part of it based on the revenue.

AUDIENCE: It depends on the budget and the cost. But then the success rate of each trial depends on how good the pool of candidates.

HAZHIR OK, so basically, this model's modeling something else. This is not modeling the stock adjustment problem we defined. It is modeling something that is important and interesting. But in light of how it is diverging into other areas, let's not spend too much time on this, not that this is not an interesting problem. Just then you don't know what is happening inside this one because that's not the problem you have thought about, so you don't get as much out of it.

AUDIENCE: It was something else, so I just took the wrong--

HAZHIR Yeah, so reading the problem definition is a good starting point. I'm just joking, but I appreciate getting us to see some interesting additional ways of looking at this. So let's look at Kathy's. This is Kathy's.

So again, fairly standard formulations that we already have seen. So for failing each-- or for success in each range, you have the success rate and the fraction, that pass. So this is P2 pass fraction multiplied by drugs divided by P2 time. And this would be 1 minus pass fraction.

So this is very similar to Alban's. So Kathy has not created a separate variable that is total drugs exiting this phase, just has combined them. I don't think in this model it matters. It's perfectly fine.

But in some other settings, it is good to have that total explicitly defined. You may use it in other variables.

AUDIENCE: Which total, I'm sorry?

HAZHIR So total drugs leaving phase II, which would be the drugs divided by phase II time. And then that would go into
RAHMANDAD: entering and failing multiplied each by the pass fraction and 1 minus pass fraction. So you would introduce an extra variable, but then you don't need the P2 time and drug two phase to go into both of these equations. That's the alternative way of formulating it, which was what Alban had, but they are mathematically identical.

Yeah, I like that alternative A little bit better, just because it makes it very salient and clear that there is a total that is coming out. If you need to use that, you can use that. You're dividing that into two different passes.

OK, so that's good. Then my quick look at this model gives me a little bit of a pause about equilibrium because I see initial drugs in P1, P2, P3, and these initials don't have any inputs into them, which tells me the model is not put into equilibrium analytically. It just has some ad hoc initial values used. So I assume that's the case.

AUDIENCE: Yeah, I can solve. And it might be because I did this aggregate thing. It was not working out.

HAZHIR Yeah, we can look at the other parts now together. So that is the equilibrium challenge here. Revenue is based
RAHMANDAD: on number of drugs in the market, annual revenue per drug.

One thing that I should mention, it is not conceptually complex, but something to keep in mind is that the patent length is not what is the delay in the drugs in the market phase. So the patents for drugs are typically filed just before they start phase I. And then the clock is ticking, and that's one of the reasons, actually, they can't hold the drugs too much, too long on the back burner.

So just conceptually, keep that in mind that the time in the market is the patent length minus the sum of all of these delays for the previous steps. You guys shouldn't necessarily know that. It's not an obvious fact of this market. You need to do some research on that.

So revenue is calculated here. That's pretty straightforward. Now, the revenue is creating a revenue target based on basically a growth factor.

So you look at the current revenue. You multiply it by the growth factor. And then you are adjusting towards that a smooth function to go into the revenue target.

By the way, I'm looking at these, and I'm reading the formulations, making assumptions that, yes, this is happening. So two things, one is, if I'm making wrong assumptions, please speak up. Stop me.

Second, if you are not following what is happening and why I'm making those assumptions, again, stop me and say, hey, I'm not following what is happening here. Can you show the equation? So I'm doing this to be faster and see more of the models, but if it means you get confused, don't let it go. Stop me. Alex.

AUDIENCE: On that note, after this, or at some point, could we go back to a SaaS model because I didn't understand how the physics of the pipeline worked with the subscripts?

HAZHIR Yes. Sure, we can do that. Let me go through a few of these, and then we should do that.

RAHMANDAD:

OK, so this part of the formulation, again, thinking about what it does, if you have a system that is working well, that is, it is doing what you want to do, that is, it is in equilibrium at the beginning, then having the revenue grow with this target revenue growth rate works fine. That is, it can generate a desired revenue process that grows exponentially as was specified in the problem definition.

But if there is any problem down here that makes your annual revenue not to be fully consistent, then the exponential growth will not happen the way you want it to happen, and everything falls apart. Not everything falls apart, but it becomes too hard to figure out what is happening that is stopping your desired and your actual to match each other.

So as such, even though this is fine, and it is actually, in some ways, more realistic because usually companies look at their current revenue and then make adjustments for what they want to see, for the purpose of this exercise, it's probably better, is cleaner to have an exogenous goal that is growing exponentially, just as Alban had with that exogenous input and some initial value. Or some other version would be fine.

So this is just, again, nothing wrong here. In fact, conceptually, even more realistic but will make your analysis harder when you're doing it this way.

AUDIENCE: You have a fully exogenous goal, though. Doesn't that sound-- disconnects as lot of what you're actually almost target-- I mean, the idea of exogenous goal growing by 10%. You have problems in the system or something. It feels like that is not realistic. A company's not going to just shove way, way more exponential growth.

HAZHIR Absolutely, so in that sense, you're absolutely right. And that's why I'm saying this is more realistic in practice.

RAHMANDAD: But if you do it that way, then you can see whether your policies allow you to track an exogenous goal of growing 5% per year or whatever it is.

But if you don't do it exogenously, then whatever problem in your supply chain adjustment ends up changing your annual revenue, it will now be built into your goals, and therefore, it is much harder to see whether you can, with your equations, get to the target of adjusting the stock so that it can grow exponentially. That's the only reason to do it that way. OK.

So then we have the desired drugs in the market. You compared that with the drugs in the market. This is the adjustment for the drugs in the market.

Then you are doing this interesting thing of expected loss rate. That is, basically, you are looking at all of the loss rates from the three, four different stocks. And you're saying I need to replace for those losses. So I need also these numbers to go into the beginning of the system.

So that idea makes sense for the case where you have equilibrium. You don't have growing stocks. But why doesn't it make sense for when you have growth?

AUDIENCE: You would expect a growth pattern in those expected loss rates. Well, there'll be [INAUDIBLE].

AUDIENCE: Even when we don't have growth, it's like a similar formulation in the desired supply then because everything is being multiplied by the delay, so it grows exponentially.

AUDIENCE: Yeah, it does grow. I couldn't get it not to grow.

AUDIENCE: But you need to add--

HAZHIR So this will grow exponentially because you have built in a reinforcing loop in the system that says, drugs in the
RAHMANDAD: market multiplied with some growth rate. So that's not the question. The question is, can you match a desired growth rate exactly in which you actually don't need to adjust your stocks?

That is, the value of the stocks are endogenously getting the right value. So in the traditional stock adjustment model, you have these adjustments of stocks that go up and down if the stock is out of the equilibrium path.

But as soon as the stock is adjusted to the equilibrium path-- with a step function, it does that after a while-- that adjustment shuts off. It's not doing anything. The stock is now in the right place, but that's with an equilibrium system.

Now, can you do it that, when it is growing exponentially, the stock is always on the right track? That is, it matching the desired value all the time? That is the real challenging task here with the growth case.

AUDIENCE: So with this won't achieve that? But if Kathy were to add in the desired expected loss.

HAZHIR Very good, so basically, for this to work, you actually need to have some adjustment that says, OK, the things
RAHMANDAD: that are lost here in the exiting market, to replace those folks, I need to start a lot more because I'm starting today.

What I'm replacing is what will be exiting 10 years from now. And therefore, I need to account for how much more will be exiting 10 years from now.

AUDIENCE: OK, so let me make sure I understand. So the problem is that, starting-- a drug failing P1 is a completely different probability than a failing exiting.

HAZHIR Not about the probability of failure. So let's assume there is no failure to keep things simple. This is about the
RAHMANDAD: growth.

The failure comes in. That has its own issue, but it doesn't have a problem in your formulation. Failure is actually accounted for in your formulation.

What is missing in your formulation is the possibility of growth. So let's break that down into these two pieces-- failure rates, success rates, failure rates. Because you have your outflows accounted for-- so you have your accounting for every outflow here, you are replacing into the system how much you're getting out of the system.

Think of a stock that includes all of these four together. If you're replacing all of the things that come out of it, you will be in equilibrium once you have adjusted for the stocks to be in equilibrium. So then this is not a problem.

That is, no matter what your success rates. This should work in equilibrium. So that is OK.

The part that is not working well is, now, if you are growing exponentially-- so let's say I'm growing, doubling every year, OK, and it takes four years for starting something until it comes out of my system. In fact, it takes more than that, but let's say four years. So it comes out of exiting market and even if we didn't have any failures to keep things simple, so it's a one-way route.

So if I'm exiting right now two drugs per year, in four years, how many drugs per year do I need to be exiting?

AUDIENCE: 16.

HAZHIR Yes, six-- no. 32 or 60? Yes, yes, because 2 to the power of 4 multiplied by 2, so that's 32.

RAHMANDAD:

So you need 32 drugs to be coming out four years from now. And now I'm discretizing. This is continuous. There is some numerical differences but conceptually the same.

OK, so I need to start 32 drugs for the two that I'm exiting today because what is being replaced is actually what is going to be coming out four years from now, which needs to be 32, not two. So your formulation only replaces two for those guys. So that is for exiting market.

Now, for failing P3, the number is different. It is not going to be 32. If each of these phases was one year, then it would be 16.

That is, if you were exiting anything from failing three, for each of those, I needed to exit-- to enter 16 into the system that three years down the road-- not for each one, for each two. For each one, it would be 8. That's the same going backwards.

AUDIENCE: OK, so to fix this, the expected loss rate should be like a growth in loss rate.

HAZHIR Exactly.

RAHMANDAD:

AUDIENCE: I get it now. Thank you, yeah.

HAZHIR Yes, so is that clear? That is really at the heart of capturing the growth process here. It wouldn't work without

RAHMANDAD: having that factor into the system.

But other than that, is for equilibrium, this should do fine. That is, you have an expected loss rate. You add adjustments for different stocks.

Now, adjustments for different stocks. The way Kathy is doing it is saying, OK, I'm adding up all the supply lines. I'm comparing it with the desired supply line. And where do you get the desired supply line? You're getting it from the expected loss rate, plus--

AUDIENCE: There's a switch for the formula. There are two options.

HAZHIR Oh, OK. So let's see, the formula switch. Expected acquisition lag multiplied by desired acquisition rate or

RAHMANDAD: expected acquisition lag multiplied by expected loss rate. So tell us what you were thinking in doing this formulation.

AUDIENCE: So the--

HAZHIR So basically, you have these two drivers either expected loss rate or expected-- desired acquisition rate.

RAHMANDAD:

AUDIENCE: Yeah, and desired acquisition rate is the loss plus--

HAZHIR The sum of those two, OK, perfect.

RAHMANDAD:

AUDIENCE: Essentially, it's including-- you're either including the adjustment for drugs and market, or you're only looking at those--

HAZHIR OK, perfect. So is it clear for everybody what Kathy is doing here? Basically, she is accounting for the two

RAHMANDAD: formulations we discussed in Alban's model, where you either account for the stock adjustment in deciding your entry or replacement or desired stock values for the next phases or not.

You just look at the-- so this is nice to think about the two explicitly and have a switch that says, I could look at it or not or have some intermediate value. So this is a good reflection of what you were thinking about. It works.

As I said, I'm probably more towards not accounting for that. OK, so that's fine. But this expected loss rate-- go ahead.

AUDIENCE: Not accounting for which.

HAZHIR Not accounting for the adjustment for drugs in market, that is, I don't know, turning on or off. But this formulation

RAHMANDAD: has some other challenges.

So if you are having a desired supply line total that is coming from these four different outflows multiplied by total lag of three of these stages, how does it work? What is it exactly doing this desired supply line?

Why should it be the same as the sum of desired value for the phase I, phase II, and phase III? Yes, why? Why would it be?

Because the logic you are using or the assumption your model is making is that the desired supply line, which is the sum of desired in phase I, desired in phase II, desired in phase III, equals the outflow of the four stocks multiplied by this acquisition lag, which is the sum of the time in those three stocks. Why is that the right formulation?

Which I think it is not. I don't think it actually works out. So this is basically, I don't know, some heuristic that came into your mind. The challenge with this heuristic is actually you're trying to do something much harder that is come up with a single total desired supply line.

Getting to that without calculating the desired for phase I, II, and III is very hard. I mean, basically you have to calculate desired phase I, desired phase II, desired phase III, then add them up. You can't do it separately.

And the desired values are the really challenging parts in this case because those are the ones you need also for equilibrium. So to calculate equilibrium, you need to put them at the desired value. The desired should be driven from the upstream from where you have the desired total drugs in the market. OK, so Alex.

AUDIENCE: What is the issue with agglomerating them all together? Why do you need to consider every transitory stock separately? [INAUDIBLE].

HAZHIR You can't write the formulation for it. Now, if you wrote the formulation for it or in whatever way, combining them
RAHMANDAD: into one step and just looking at the sum of all of them versus the desired sum of all of them and dividing that by some time constant, is OK. There is nothing wrong with that conceptually.

But to get to your desired total, you actually have to find the desired for every item. So that's where things don't work in this formulation.

AUDIENCE: I think I figured out.

HAZHIR OK, we can check out your formulation as well. OK, so that's that. Then we have desired supply line.
RAHMANDAD:

So you have adjustments for supply line. The rest is fairly straightforward. So that's replacement.

So we had one request to look at [? Hassam's ?] model again, just to get-- this one, yes-- to get how the stock inflows work. And basically-- so initiation of drugs, that's the key formulation that we haven't looked at. Here is coming from a budget.

And then the budget is for each phase. And the budget for each phase comes from a budget share. But it doesn't account for availability of drugs for phase-- so let's say I want to start phase III.

AUDIENCE: You don't have any candidates.

HAZHIR And I don't have any candidate. Is that captured in this feedback loop?
RAHMANDAD:

AUDIENCE: [INAUDIBLE] that version of them can start drugs for phase III, which is unrealistic. But the success rate would be zero. So I'm repacking the availability of good candidates and success rates.

HAZHIR So that's not generally a good way to do these things because it will-- you are basically saying, let me change the
RAHMANDAD: success rate, but let me start drugs. OK. And that's not how the real world works, basically.

AUDIENCE: Shoestring budget when you start those?

AUDIENCE: It does.

HAZHIR Yeah. Part of it is that it does. I mean, you could always make additional auxiliary assumptions. I go and acquire
RAHMANDAD: a firm that has done phase II trials and now starting something in phase III. So you could come up with those explanations.

But if you keep everything from your pipeline, you definitely need a feedback from drugs that have passed the previous phase. Then you have to define a maximum rate of starting new drugs based on a minimum time to start a trial and then compare that with what you can through the budget and start.

AUDIENCE: I was formulating the success rate. So I just skipped that.

HAZHIR Yeah. Yeah, anyway. So we could spend more time on this. But I think--
RAHMANDAD:

AUDIENCE: So drugs don't flow from one place to another?

HAZHIR They are not. In this model, it's actually there is no endogenous flow here. Yeah, that is confusing.

RAHMANDAD:

And actually to do it right, you will need these shifting of subscripts. That is, you remember in the population aging things that we had the population of the previous age feeding into this. You would need that, and maybe you have it somewhere. Yeah, so you have seen examples of that shifting.

You cannot have equations that only use the full subscript in them because there is a shifting. So phase I has a different decision rule because you can start a lot whereas phase II depends on how many phase I has passed and is in the menu for starting phase II.

AUDIENCE: So there's no aging chain here?

HAZHIR There is no exact aging chain. I mean, for each phase, there is an aging chain, but there is not a continuous
RAHMANDAD: aging chain.

AUDIENCE: You just approximate it, so to speak, by changing the success rate, where if there's zero in phase I, then you try to start-- but you try to start phase II, but none of the phase II that you start will--

HAZHIR Yeah, so this is not working. Basically, there is also the other problem that if you are starting something, at least
RAHMANDAD: you have to drain it out of the successful ones in that phase to get to this continuous aging.

That is, if I'm starting a phase II, then the drug past trial phase I, I mean, you can keep it in that stock. You just call it-- yeah, but if you wanted to have the feedback, then you couldn't use those drugs that have passed phase I but have already started phase II to restart them. So you needed to drain those into a different stock.

AUDIENCE: I am not following the logic. I don't want to be taking too much of time [INAUDIBLE].

HAZHIR Yeah, so the logic is that if you are starting phase II out of a drug that you have already passed in phase I, you
RAHMANDAD: want to drain that drug past phase I, either into a separate stock or into a cloud because, otherwise, next year, you want to start another phase II. You go and count how many you have in past phase I.

AUDIENCE: The firm can actually do that, right? Can you start a phase II trial on that drug this year? Another one--

HAZHIR But not infinitely. So, yes, you can have a parameter that says how many times.
RAHMANDAD:

AUDIENCE: But so what I've done is that I've-- depending on how much initiation of phase II I have, I change the observation rate of phase I. So if I'm starting a lot of trials for phase II, the drug that I have in phase I of the past phase I, they will go obsolete more quickly?

HAZHIR It wouldn't work because there is a one-on-one thing. That is, each drug that you take from phase I is feeding
RAHMANDAD: into one drug for phase II. Now, you may go into the more complex case that I can do it five times. Then you have to drain it 0.2 of it or something.

But with the time constant changes that change the obsolescence rate, you can't correctly account for, OK, how much of it I have drained and how much credit still I have. It wouldn't remain internally consistent. So that becomes a problem down the road.

Let's not spend too much time on this. But I think that was a good conversation because you need to think about these-- biggest lesson for this here is follow the physics. Don't try to bring alternative ways of capturing a feedback, whether it is through obsolescence rate, whether it is through changing the success rate.

Just follow the physics. Otherwise, it will blow up. OK, good.

Who wants to look at-- wants us to look at their model? Do you want-- sure.

AUDIENCE: I think it's pretty similar. It's the next one.

HAZHIR
RAHMANDAD: To the right. OK, so we have the same a time failure rate. So that's very similar to Kathy's.

And then we have the initial values that are hard coded. So don't hard code initial values. Even if you're putting it into equilibrium, put a desired initial-- I mean, if you want to have a numerical value, put it initial because, otherwise, you have to come into this equation and change it. You can't change it quickly into your-- so that's generic suggestion.

Then you have patent expiry, time on market. You have very similar idea here for-- no, actually, your desired annual revenue is exogenous. So it is happening from some initial value that you have hard coded here and with target growth rates.

Then this gives you the target drugs with your revenue. You look at the gap. That's the adjustment for ordering that comes from drugs in market.

So this, with a total success rate, gives you desired attempts. And then--

AUDIENCE: How does is the success rate impact the adjustment order? You divide it by--

HAZHIR
RAHMANDAD: Yeah.

AUDIENCE: Originally, the success rate was just the percentage. And last minute, changed it to [INAUDIBLE] close out. I don't really know why. [INAUDIBLE].

HAZHIR
RAHMANDAD: So success rate, I think, parameter should be the right formulation because, yes, the flows here would make it a mess. You can't handle it.

AUDIENCE: [INAUDIBLE] feel like the fail rates up there [INAUDIBLE].

HAZHIR
RAHMANDAD: Yeah. Yeah, the failure rates are the correct ones. They should be just-- well, so multiplied-- you should multiply the success rates to get the total success rate. So if you-- because they are--

AUDIENCE: Well, it used to be the multiplication of all the 1 minus--

HAZHIR Yes, that's correct, yeah.

RAHMANDAD:

AUDIENCE: Yeah, my main issue is I just completely ignored time at some point because if there were optimizations to the path of getting the drugs to the phases, the drugs that are currently in markets patents are going to expire in two years or whatever. But these new drugs are going to be on the market for 18 years.

Oh, yeah, the success [INAUDIBLE] because every time I wanted to try and do the effective entry on quality, but every time, I tried to make a formulation of it, it was a simultaneous formulation. And I couldn't figure out how to do it. I think I should just maybe stop [INAUDIBLE].

But, yeah, I have a lot of issues with [INAUDIBLE]. And then what you were saying earlier, which is the maintenance drug rate has to be correlated to the target group. I didn't know that [INAUDIBLE].

HAZHIR Yeah, so the growth is not captured here. But let's just track what is happening with the start rate right now. So

RAHMANDAD: quality, let's not worry about it.

There is a max attempt based on budget. Let's not worry about it. So it is the desired attempts that is driving it. And it is coming from the patent expiration, which is important.

There is this alternative drug thing, I don't know. Yeah, yeah. OK, so there is an expiration divided by the success rate. So that's the right formulation to get in the equilibrium without growth the number of new drugs that you start. So that's good.

And then you have the adjustment based on the drugs in the market. That's also fine. Although, let me think.

AUDIENCE: Is there no adjustment for the pipeline?

HAZHIR Yes, so there is no adjustment for pipeline. So that's missing, definitely. I'm also thinking whether the adjustment

RAHMANDAD: ordering here for this needs to be divided by the success rate.

So right now, the role of this success rate division is basically making this time constant smaller, making it faster. You can look at the equation. It is the gap divided by success rate divided by time to market because time to market is a parameter. It is as if you are making that parameter shorter, smaller.

Because this is a number between 0 and 1. So as such, it doesn't have a qualitative effect on-- so I'm not really following what exactly you wanted to do because the success rate is-- if you think it is impacting the desired level of the stock, it should be operating on the target draw queue, which is not, and which is fine because you don't want it to. Your target shouldn't be affected by the success rate.

AUDIENCE: I think my idea is you have-- however, so target drug queue is, how many you need to be at this revenue?

HAZHIR Yes.

RAHMANDAD:

AUDIENCE: And then the gap is, obviously, the difference between this target and the current drugs. And the reason I divided it by the success rate was the idea like, OK, well, if the gap between how many you want and how many there are is 10, the success rate is 10%, then you should have 100. So that was my idea of dividing by success rate because then you get like, OK, you need 100 drugs to be going in to the pipeline, and then you divide [INAUDIBLE] pipeline.

HAZHIR Yeah, but this is a little bit of a stock and flow confusion because, as you said, the time is missing because what
RAHMANDAD: is 100? Its per unit of time is the adjustment rate. So it is basically you're saying, I'm adjusting it faster.

AUDIENCE: Yeah.

HAZHIR OK, so basically, this formulation works for adjusting the drugs in market with this caveat of what success rate
RAHMANDAD: really shouldn't come into this formulation. It is working fine for replacement of patent expiry under equilibrium conditions, but not in the general case.

It doesn't have adjustments for P1, P2, and P3. So that's another challenge. But otherwise, it has the basics of the stock adjustment formulation we are familiar with. Good.

AUDIENCE: So what is the issue with having a success rate in the adjustment order? Because I get that it essentially does the same thing here as the time to adjust, and it just makes you go faster. But I feel like, I mean, at least for me, it makes sense, exactly what you said.

You want you want to be starting more drugs than you need in the end because the vast majority will fail. I guess, for me, personally, it just-- and I'm not in this space, so what does it matter? But when I'm formulating, it makes a lot more sense for me to think about what I need to start more [INAUDIBLE].

HAZHIR Yeah, it's a good pushback. That is, the time to adjust can be thought of as having these two components. One is
RAHMANDAD: kind of how fast I want to close the gap. The other is if the gap is bigger, I need to start a lot more at the beginning.

So why not just divide it by the success rate? Yeah, I buy that. So I take back my comment that you don't need this.

I mean, it's OK not to have it, but there is conceptually a good reason to do it. And I think your explanation was aligned with that. OK, good. Let's see, who else? Volunteers?

AUDIENCE: I'm sorry, just one more question about this. Isn't the [INAUDIBLE] adjustment to support supply line problematic? Because, I mean, just in the basic stock management-- if you don't adjust the supply line--

HAZHIR Yeah, things don't work. So this doesn't have the adjustment. So this will not do all of the nice things that--
RAHMANDAD: basically, it is ignoring the supply line. And therefore, it will create oscillations that you don't want to see. So, yes, this does suffer from that.

Sure. OK, good so you have two views for input. That's nice.

Let's go to the basics again. Stocks and flows are standard removal multiplied by success and 1 minus success. All of that is fine.

You are using the same success fraction. That's OK. Conceptually, they are different. And in reality, they are also somewhat different. But they are close enough that you can also combine them.

You have the desired stock from the desired annual revenue. And then you get the annual revenue. All of that is good.

And we talked about this patent duration to account actually for all of these other times, nothing important here mathematically. This doesn't make a difference. OK, adjustment for drugs on market is desired stock, market adjustment time.

And then you have expected expiration date. Rate that creates desired market advancement. So this is for equilibrium. So this is very similar to Alban's formulation, I think.

And then that gives you the desired phase III. Good, and then the desired phase III goes into the initiation here. And the way you formulated the desired phase III, let's check that out.

So it is desired market advancement, average timing P3 divided by P3 success fraction. So that's good formulation. Does all you need to do for non-growth case. This--

AUDIENCE: This won't grow. Or it grows, but--

HAZHIR Then there will be a steady state gap for the growth case. And then this then goes backwards. Very similar, I
RAHMANDAD: think, all of them will do the same idea.

So you are also using Alban's version where what comes from the previous stages feeds into the desired levels of the stocks. So it can push them up and down notably as a result of that, which is, as I said, debatable whether that's the best formulation or not, but it's OK.

And then let's see, I think it's all-- the rest is a standard. We have talked about the ideas.

AUDIENCE: Yeah, I actually don't know if I have it.

HAZHIR So let's simulate it. We haven't simulated much yet. So this is actually a good time to start simulating.
RAHMANDAD:

So this starts from equilibrium, great. And then we can-- what's that?

AUDIENCE: [INAUDIBLE] has all the inputs.

HAZHIR Yeah, but another way is to just change the annual desired stock or annual revenue. So I'll just do this. So I'll say,
RAHMANDAD: let's do a step change. Go 20% off.

So drugs in the market is the key thing because you want that to be stable. Now, this does create oscillations for drugs in market. And part of it is-- so if we don't adjust the market as fast, it actually helps.

So this is one of those places. Is it visible? Or is it too small?

So you see, if we go smaller on this market adjustment time, we get into a full-fledged undamped oscillations. And as soon as we increase that a little bit, things become pretty reasonable. So I mean, you still see the oscillations back there, but much smaller. So can anybody come up with a hypothesis for what is happening here?

So we have full adjustment for the supply line. So in that sense, we are not ignoring the supply line. And we are doing it with decent formulations all along. Why do you get cases where you still get a lot of oscillation? Alexander.

AUDIENCE: What is the adjustment time for the supply line?

HAZHIR So adjustments times are 2. So they're all 2, I think.

RAHMANDAD:

AUDIENCE: I have a hyperparameter.

HAZHIR Yes, that is adjusting. But any hypothesis?

RAHMANDAD:

AUDIENCE: Oh, [INAUDIBLE] to a short-term disequilibrium.

HAZHIR Can you, can you speak up again, Alban?

RAHMANDAD:

AUDIENCE: You overreact to a short-term disequilibrium?

HAZHIR Yes, how do you overreact to a short-term disequilibrium?

RAHMANDAD:

AUDIENCE: Because your adjustment time is too small. The timescale is too small.

HAZHIR So this is actually where the formulation issue that I mentioned is really creating its problem. So if you're

RAHMANDAD: adjusting the next stock, desired level of the next stock, based on adjustment in the current stock, now, if the adjustment in the current stock is large, now it requires, even a larger adjustment in the previous stock, and that will require even a larger adjustment in the next one and so on.

So it creates this cascade of adjustments that, under some time constants, for these adjustments, can actually create their own oscillatory mode of behavior. So my pretty strong guess is that they will go away if you didn't have this formulation that adds up the desired for replacement with the desired changes in each stage for the stock.

So this is actually a good example of where the two formulations-- and Kathy had the two extremes on a switch that you could play with. We don't have a switch here, so it's a little bit more work to get it to see that difference. But that's the idea.

AUDIENCE: Does it depend-- well, I asked about the supply line adjustment because it seems like, when you go over it, when you go above 2, then the oscillations get damped. So like it just seems odd but in real-- And that's not how Jason parameterized it.

So it would just seem odd that in real life you're trying to adjust your-- well, I guess that's what happens in real life. And that's the whole point of the growing supply line. You're trying to change the drugs on the market really quickly, but you're not changing how many drugs you have in supply as quickly.

Because when you had the oscillations for the drugs in the market [INAUDIBLE] sometimes one but the adjustment for the phases was twice as long. It was two years. So it just seems-- isn't that part of it as well? It's the balance of the adjustment times for the--

HAZHIR Yeah, so the real difference is that we are correcting two different-- through two different channels. One is the
RAHMANDAD: channel for replacement that needs to be corrected across all of the intermediates' stocks so that they are consistent with our ultimate outflow. The other is we are adding another correction that is saying, all these intermediate stocks need to go up and down to also adjust for the adjustment of the upstream stocks.

AUDIENCE: So in this case, so just to be extremely operational, the desired phase III in this case should just be the expected expiration date multiplied by the, whatever, the time.

HAZHIR Yes, divided by success rate.

RAHMANDAD:

AUDIENCE: And then it's the same for all the--

HAZHIR --for all the next ones. In fact-- yes, exactly. That's it.

RAHMANDAD:

And it is also. Yes, it could be the expiration date. But this is another important conceptual difference.

That is, better solution is not getting it from the patent expiration date, but get it from the desired stock of desired drugs on market divided by the patent duration. You see the difference? So--

AUDIENCE: Yeah, instead--

HAZHIR Yes, because this is the current rate, and it is not the desired rate. So it will wait for that stock to be adjusted to
RAHMANDAD: get it correctly. Is that clear?

AUDIENCE: So just to summarize, Alexander's point was those desired levels, each phase should not depend on the desired level for the prior phase. This way you avoid that accumulating.

HAZHIR Yes.

RAHMANDAD:

AUDIENCE: I think it's more isolated to each.

HAZHIR Yes, yes, exactly.

RAHMANDAD:

AUDIENCE: They don't see each other.

HAZHIR They don't see each other. Yeah.

RAHMANDAD:

AUDIENCE: So the desired for phase II, for example, is that case. It's just based off of the failure rate for phase III?

HAZHIR Not failure rate. You want it to be based on the desired replacement rate that you calculated. So here, let's say
RAHMANDAD: this is the desired expiration rate, not the expected. It is the desired based on the desired stock.

Then you use that desired expiration rate to calculate desired market advancement. That's fine. You don't add this adjustment for drugs on market into market advancement.

Then this desired advancement goes into the next one. You just don't add this adjustment for phase III. So all of the equations remain the same, except that these adjustments don't come into this desired thingy.

And then, at the end, you add all of those adjustments into a separate component that goes into the development start rate. So right now the development start rate is max of 0 and this desired DSR so that it doesn't go 0. That's good.

Then, in this alternative, you would have this desired DSR plus all of those stock adjustments. And now going back to your formulation, we could, for those, incorporate those success rates as well to speed that up.

AUDIENCE: Wait. So wait, I thought you had to include the success rates at this point because I don't see where the--

HAZHIR So the success rates are incorporated. So the way they are incorporated is that, at each step, the desired
RAHMANDAD: advanced to the next phase is getting feedback from the success rate.

AUDIENCE: Yeah, I'm adding in the expected failure.

HAZHIR Yes, it is coming from the expected failure. There is expected failure. Yes, this is the expected.

RAHMANDAD:

But this is the problem. This is another problem. So this should not be getting input from the expected P3-- OK, let me see what's the equation here, sorry. First of all, why does it have max 0 here?

AUDIENCE: Can't go backwards. Or you can't--

HAZHIR You're not yet affecting any flow. Why do you impose the max 0 at every step?

RAHMANDAD:

AUDIENCE: What do you mean you're not affecting-- I see. Because--

HAZHIR So you have actually three different things. So you have the expected P3 failure. You have desired market
RAHMANDAD: advancement. And then you have the adjustment for phase III. I see.

OK, so the way Jason is capturing it here is that he's capturing the failure rate inside this formulation. So he's saying, OK, there is the-- sorry, leave aside adjustment for phase III. You could throw this out.

You have desired market advancement which is the on flow. And then you have expected failure phase III which is another flow, which is going out. But note that there is a little bit of an internal inconsistency between these two flows.

The second one is coming from your ultimate expectation of how many things are going to be expiring. This desired market advancement is coming from the current level of the stock being failed-- stock going into the failure rate.

AUDIENCE: They're both coming from--

HAZHIR This expected P3 failure is coming from the next-- sorry, the desired market advancement is coming from the
RAHMANDAD: next stage.

AUDIENCE: Yes.

HAZHIR OK. And in fact, with the correct formulation, it wouldn't be coming even from patent expiration. It would come
RAHMANDAD: from the desired expiration rate. So this is anchored into your ultimate goal. That's good.

But here, you are combining this component that is anchored to your ultimate goal with a component that is anchored in your current level of stock. So if my current level of stock here is 0, and therefore I have no phase III failure because of this equilibrium dynamics, I'm going to affect my replacement rate badly. That is, I'm going to under-replace.

And you don't want that to happen. In fact, you actually want to increase-- so--

AUDIENCE: Why you get that [INAUDIBLE].

HAZHIR Yes, so this might be another reason for the oscillatory modes. You have this built-in bad responses because they
RAHMANDAD: don't account for your ultimate goal. They are looking at what is currently being exited and only replacing that much.

So the right way is to get your desired market advancement. Divide that by your success rate for this phase. So when you divide that by your success rate for this phase, you're accounting for the desired level, and you're expanding for the failure rate.

Now, in equilibrium, they both give the right answer. And that's why you didn't detect it when you were doing the equilibrium analysis. But these oscillatory modes are coming out of these two issues. I'm not sure which one is more important. You actually need--

AUDIENCE: [INAUDIBLE] by the success rate.

HAZHIR Yeah, would resolve the issue.
RAHMANDAD:

AUDIENCE: So that would-- so you would divide by the success rate for the desired P3 advancement?

HAZHIR Yes, I would divide by success rate for P3. Yes.
RAHMANDAD:

AUDIENCE: So for the-- OK. And then--

HAZHIR And then the next one, desired success rate for P2 and so on.
RAHMANDAD:

AUDIENCE: And then that's all you do going down the chain.

HAZHIR Yes.

RAHMANDAD:

AUDIENCE: OK, because then-- I see.

HAZHIR This is without growth. We should get to the growth. But I think it's a good time to take a break and look at the

RAHMANDAD: growth after we come back. Yeah, go ahead.

AUDIENCE: And then the initial value of the mineral stocks would be the desire.

HAZHIR So the desired phase IIs that are being calculated are good. Once you have this desired advancement, you just

RAHMANDAD: get that. And yeah, P3 advancement should give you your desired two.

You just multiply that by the time constant divided by P2 success fraction. And you can do it for every single one.
Yes.

AUDIENCE: Wait, sorry, how is that-- so for phase I-- oh, I see, I see.

HAZHIR Let's look at the phase I. The desired phase I is coming from desired P2 advancement times the average time in

RAHMANDAD: P1. So that is the Little's Law, except that you need to expand it for the fraction that fails.

AUDIENCE: But then it's not-- but the desired levels aren't changing any of the flows.

HAZHIR The desired levels are not changing these flows yet. They will be added. So all of these adjustments need to be

RAHMANDAD: added together as a total stock adjustment that would be added to this desired DSR.

AUDIENCE: Well, no, you were saying that we shouldn't add the adjustments because--

HAZHIR No, no, I was saying, at the very end, they should be added.

RAHMANDAD:

AUDIENCE: They don't need to be--

HAZHIR They don't need to be added in the intermediate steps. In the intermediate steps, they'll mess things up, but they

RAHMANDAD: are important. You do want to adjust for those stocks.

So they will-- I'll show you a version that has that when we come back. OK? Good, let's take 10 minutes.

Let's look at what you have here. Let's not go through the last year thing. It's traumatic.

AUDIENCE: Well, well, I bring it-- I bring it up because I think [INAUDIBLE] able to put it in equilibrium just by treating all the stocks together.

HAZHIR Ah, so because this one doesn't have equilibrium, you're saying.

RAHMANDAD:

AUDIENCE: Yeah, this doesn't-- this one doesn't go to the--

HAZHIR Yeah, but I think, last year, we weren't holding you for exponential growth trajectory either.

RAHMANDAD:

AUDIENCE: So I don't-- yeah, yeah. And I don't do the exponential growth either. But I'm just saying that, unlike the cascading one, which is successful in [INAUDIBLE] equilibrium, it was a lot more complicated. But I just thought it might be instructive to see how I did it by putting them all together and those two [INAUDIBLE].

HAZHIR OK, so maybe I'll check that as well. You have it on the folder. OK.

RAHMANDAD:

AUDIENCE: Just like D2 generally.

HAZHIR I see, I see. So let's then take a quick look at this one and then maybe look at the other one. So this is simulating

RAHMANDAD: as well.

So again, basic backbone, the same as before. You have the drug expiry. That is being added to adjustment for drugs in the market to create these desired drug development rate, which then is--

AUDIENCE: So I tried to treat all the drugs in development as a single stock, which I realized without a lot of subtleties doesn't work and which is why this model doesn't go-- it goes into a steady state. But it doesn't reach the desired level of drugs. So the desired total number of drugs is just the desired development rate times the time to develop the drugs.

HAZHIR Desired total drugs in development, so drugs in development requires accounting for the failure rates to do it

RAHMANDAD: right. So just looking at the-- so you can't get the desired total drugs in development by multiplying desired drug development rate and time to develop drugs.

AUDIENCE: So I try to do it-- so again, I don't think I did it successfully in this version, but I tried [INAUDIBLE] later on, which I call the drug start rate with buffer. And then, there, that accounts for the failure rate.

HAZHIR Oof. OK. So wouldn't work well because if you are trying to adjust the stocks, you need to adjust the stocks.

RAHMANDAD: Otherwise, you are doing something that is hard to conceptually know what exactly it is. Yes, it adjusts for something, but it is not exactly doing the adjustment for stocks that you want it to do.

And then you are adding the failure rates, which is similar to-- OK, this is a complex formulation. Let's see.

AUDIENCE: So what this is is the first term is you-- I'm taking into account the failure rates. It does the same thing as taking [INAUDIBLE] out the failure rates when I determine the desired drug development rate and the desired number of drugs in development.

And then my thought was like, OK, you want to replace the drugs that are failing, but you want to take into account the fact that there are failure rates along the way. So to replace the stage 1 drugs that are failing--

HAZHIR OK, just so fraction succeeding development is the multiplication of the three success rates?

RAHMANDAD:

AUDIENCE: Yeah.

HAZHIR OK, so indicated drug start rate, what is that? So indicated drug started was the total coming from two factors.

RAHMANDAD: One was the stock adjustment thingy that is not quite right, but let's put that aside.

Then there is this the-- there is the replacement. And then there is the drug adjustment for the drugs in the market.

So in the case that you have only the replacement, the simplest case, in the indicated drug start rate, dividing that by the total success rate gives you a good anchor for the drug start rate, without accounting for growth. If you account for growth, things will not work well.

And we had that formulation, I think, in your case. In a couple other cases, we had that. In [? Oriana's ?] case as well.

Then you are adding these drug failure rates to that total start rate. Those drug failure rates are an alternative way of accounting for failures, which I think Kathy was using by looking at the sum of all of the failure rates and some of-- and the drugs with expiring patterns.

If you add all of those four together, that's the net outflow from the system. You restart that much. You keep the system in equilibrium. So then that would be another way to capture it.

Here, you are really combining the two together in a way that is not fully consistent as well. You have all these stock adjustments that are not quite right. I mean, the first part is right. The second part, as we went through Kathy's example, doesn't quite work. So this is not going to work, even for the normal getting to what you want to have in the desired stocks.

Let's open the other one that you said has some additional features we may want to look at. So this is the general version.

AUDIENCE: Yeah, so the basic idea is the same. I just built on it. And there's a bunch of other stuff that was taken from the other [INAUDIBLE] question that isn't pertinent here, like the cancellation and things like that. That's 0, I think.

HAZHIR Yeah, so the cancellation is actually an important consideration. That is, in all of our conversations, we have

RAHMANDAD: assumed the only way to get rid of a drug is wait for it to flow out of the system or down through failure. But it is actually very easy to cancel things.

So that is a very conceptually important thing that we are skipping, we are ignoring here, just to keep things simple. Now, it doesn't kick in in a situation that you are growing, and you don't have big misalignments in your stocks. It doesn't become that important.

But if you want to reduce your pipeline for whatever reason, you're just exiting market because the world is finishing or something, you can use the exit rates cancellations more explicitly. Or if you have too much in any of your stages, you can do it. So, OK, that's just something that we are ignoring.

Now, here, again, the basics are pretty much the same. You have the time to develop. So tell me, what was the equilibrium setup here?

AUDIENCE: Yeah, it's been a while since I've looked at this.

HAZHIR Yes, OK, so this is initial successful drugs in trial divided by 3 It shows succ-- So this is I'm not sure if it would do

RAHMANDAD: the trick for the equilibrium either because--

AUDIENCE: So it might not be-- yeah, it might not be initialized in equilibrium. That wasn't what I was looking for.

HAZHIR Yeah, so the initialization in equilibrium, it probably wouldn't work that well. And then there is that stock

RAHMANDAD: adjustment question. That is, OK, how do you correct for these different stocks?

You have it in the drugs in development adjustment. You are adding them up. Let's look at that.

AUDIENCE: Yeah, I think this is a relatively--

HAZHIR Yeah, so you are looking at each with a-- compared to a desire. So this is what we discussed, that you want to

RAHMANDAD: have separate desired ones for each stage. And you look at the gap between the desired and actual for each and correct for that.

So then there is the question of, what is the desired for each of these? So then you have desired-- where is desired? Middle stage drugs. No.

AUDIENCE: One to the right.

HAZHIR Right of desired drugs in development.

RAHMANDAD:

AUDIENCE: It's essentially equal to the indicated. Again, because of the other parts of the model, there was a consideration of [INAUDIBLE] budget, which I don't mean to--

HAZHIR So this needs us to understand a little bit more about what was happening. I don't remember the details.

RAHMANDAD:

AUDIENCE: So it's not supposed to be a constraint. It's supposed to be equal to the indicated. And the indicated-- yeah.

HAZHIR And indicated is the total-- ah, interesting. So you have this likelihood that is trying to adjust across all of them

RAHMANDAD: and give you a single desired value for each step.

AUDIENCE: And it's quite complex.

HAZHIR Yeah. OK, so I'm not going to dig deeper into this because it will take us too long to figure out what exactly works

RAHMANDAD: here. But it's not the cleanest way of doing it.

So you need separate desired values for each stock that accounts. And this one also wouldn't do the growth dynamics. OK, other volunteers?

Let's then just go and see who we haven't checked out. Jason we looked at, which is this one. This is Ross. OK, so Ross's model has the basic backbone with the start and failures, revenue.

Then you have the desired revenue that is based on a growth rate. That gives you desired drugs. And then desired drugs, let me make it a little bit bigger so that we can see things a bit better.

OK, desired drugs. OK, I need to go here and see what is happening in project. Start rate because it's a bit more complex.

Desired patented drugs at t plus capital T multiplied by desired growth rate plus 1 over patent time divided by drug success probability. Ross, can you tell us what's happening here? What's the logic behind them?

AUDIENCE: Oh, there were-- I don't think I dealt with the stock thing before, so I was trying to look at the outflow from the total system and then needed the growth part. I try to replace it in the beginning with the time difference between the whole pipe.

HAZHIR Yes. So all of that makes sense. So division by drug success probability, I think, is the part for accounting for
RAHMANDAD: failure rates. So that makes sense.

The desired patented drugs at time t plus capital T is, I guess--

AUDIENCE: Average time spent in the pipeline.

HAZHIR Yes, but desired patented drugs, this sounds like in the units of drugs. Yes. So this is like the stock that you want
RAHMANDAD: to have. Then you get that stock. You multiply that by growth rate plus 1 over patent life.

What is this? This part I can't follow. What is happening here? Can you tell us what you were thinking to do?

AUDIENCE: To add for the growth. And then the second part is to replace the outflow from the patent--

HAZHIR Yes, so 1 over patent life is good for outflow. That basically gives you the outflow. So if you didn't have the
RAHMANDAD: desired growth rate here. I could follow this for the equilibrium condition.

Then you have this desired growth rate being added to it. And the units work because growth rate is 1 over unit of time. But I'm not just following the conceptually what is happening here.

Because that growth rate multiplied by the stock of desired patented drugs, what is it telling us? It tells us, what's the rate of growth in this stock that we want to see? So it would be the net flow. So that would be the net flow for the stock.

So you are saying I'm adding the net flow for it to be able to grow to what is the outflow, which is 1 over patent time. So that becomes the net inflow that should go into it to get the outflow that allows us to grow.

OK, that makes sense. Then to get that net inflow, you need to also divide it by drug success probability. So that part works fine.

AUDIENCE: I simulated. Then it gets less and less accurate as--

HAZHIR As the time goes.

RAHMANDAD:

AUDIENCE: Yeah.

HAZHIR Yeah, so it is missing something. I'll show you some example that has this. But this is an interesting-- you had a
RAHMANDAD: good piece of idea for capturing the growth.

That is, you want the inflow minus outflow for the last stock to be the growing-- I mean, to be the net growth rate for that stock. And the net growth rate is your desired growth rate multiplied by the stock. So this is actually giving you an indication of the growth-- what you need to adjust to be able to actually grow.

But that indication alone is not going to do the job for you here. It needs to be kind of incorporated more structurally into the steps of the process. And of course, you don't have stock adjustment parts.

So for those intermediate stocks, there is no adjustment. Even for the patented drugs, there is no adjustment. So that will create another issue. Then the equilibrium initialization is not happening.

So those are things that we already talked about. So you know, good. I think that idea, we'll use it in a few minutes.

Let's see. We have looked at Ross's. Alban's we have looked at. [? Oriana ?] we have looked at. [INAUDIBLE], OK, let's look at this one.

So again, basic structure, we are in agreement. Then to look at what is happening, we have adjustments for different phases. So you have desired phase I, phase II, phase III.

You have these adjustments, and then you have the desired numbers entering the market that is coming from desired number of patented drugs in the market compared to the desired patent plus-- so this is the adjustment for this stock and expected patent expirations. So let's take a look at this formulation.

So this is basically the standard replacement plus adjustment for the final stock that we have seen. And that works fine with the caveat that this is not the desired number of molecules entering the market. This is the number that is exiting and needs to be replaced.

But to get to the desired that gets into the market, what do we need? What correction do we need?

AUDIENCE: [INAUDIBLE] It doesn't for the supply.

HAZHIR So that you are adding later.

RAHMANDAD:

AUDIENCE: You need this growth after the--

HAZHIR And let's forget about growth. The growth factor, yes, is missing, but that's not-- it needs something more basic.

RAHMANDAD:

Yeah, the success rates are missing. So if only 10% are succeeding, you need to multiply the exit rate of the drug getting out of-- expiring by 10 to start enough to get to replace the 10 that are expiring.

AUDIENCE: I incorporated the success rates--

HAZHIR In the last step? Ah, OK.

RAHMANDAD:

AUDIENCE: --calculating the desired values for the stocks.

HAZHIR So desired values for the stocks--

RAHMANDAD:

AUDIENCE: I think it's up, up.

HAZHIR OK, good. So we'll get to that. But that is not enough. So even if the desired values are correctly accounting for

RAHMANDAD: that, the replacement-- so in equilibrium, the desired stocks will have their desired values. So all that is happening is the replacement.

OK, the replacement, for every 10 that is going out, you need to start 100. That is not yet in the formulation. So that needs to be there.

Then we can look at the desired values which are very important. So the first one is easy because that is coming directly from desired revenue. Then the desired phase III trials or-- yes, phase III trials, it's getting the input from the expected patent expiration. So that's the ultimate goal, which is good.

But as we discussed, what is the problem with expected patent expirations is that it is looking at the empirical value rather than the goal. So it is adjusting towards what is already happening, which may not be aligned with your goal. So that's we saw that in Jason's model as well, accounting for that or putting that aside.

Now for this one, we care about replacing the phase III success rate and the average phase III times. So this is a good formulation. It has expected patent expiration divided by success rate gives you the total inflow multiplied by average phase III time total stock.

And then the rest are also following the same logic with the additional subtlety that now you have to multiply phase III and phase II success rates for the desired phase II. So this is important. In the version that Jason and a few others had-- I think Alban had it as well-- this cascade was happening inside the formulations, so each one was dividing by that success rate. And then the next one was dividing by that success rate.

In this version, you are doing it explicitly in each step. Mathematically the same, no general preference for one or the other. Both are good. And so you're doing it well here. It's getting the right desired levels.

And so when you get these desired levels, all of these stock adjustments down here, they work fine. They do what they need to do with the point that you brought up about the speed of adjustment. If you have a gap, you may actually inflate it to account for those failure rates that will happen as well.

That's fair. That we could add here. Doesn't have it. But that's all right. You could incorporate that mental in the phase II adjustment times, but probably better to have it in the success rate.

OK, so this is good. I think the stock adjustments are working very well here. The part that is missing is the correction for the success rate for the replacement. And then the other thing is the growth that I think every formulation so far has missed that.

OK, let's now look at maybe one that does have the gross formulation. So--

AUDIENCE: I also have a good formulation in there. But--

HAZHIR So what do you do for the gross? Tell us.

RAHMANDAD:

AUDIENCE: I calculate the average revenue with the slope.

HAZHIR Yes.

RAHMANDAD:

AUDIENCE: I added the desired growth rate. But the model doesn't behave the way we expected.

HAZHIR Yes, so you are calculating the average revenue from what is the current revenue. Then you are getting a target

RAHMANDAD: to get it to grow. And then, based on that, you get to the desired number of patented drugs.

So that's very similar to, I think, Kathy's formulation that basically used the current revenue to set the target. And as we discussed there, that's conceptually correct and fine. It is closer to the real world than the alternative that makes the revenue target exogenous. It creates impetus for growth, so you will see growth in this model. But you wouldn't see matching of the desired and actual with these formulations.

OK, so let's go to something that I built the other day.

AUDIENCE: Can I ask you a question?

HAZHIR Sure.

RAHMANDAD:

AUDIENCE: In terms of matching to the growth, even if you didn't have all of this top drug pipeline, it's just the stock cannot-- because it's always growing, does it even reach [INAUDIBLE]?

HAZHIR So that's the hard part. How can you set the initial-- the initiation rate so that it does match-- so that's the

RAHMANDAD: challenge. That's the whole point of the-- yeah, it is doable. If the question is, is it doable? Yes, the answer is yes.

So this is what I put together yesterday. So here, you have basically the same basics very much. You're now all familiar with it.

The desired revenue is exogenous. I'm right now driving it as a stock with some desired growth rate. You can drive it with an exogenous input like Alban's equation, which gives us desired drug. So all of that, very standard.

Then we get to the desired adjustment for drugs in the market and desired adjustment for P3, P2, P1. And then you add them up as the total stock adjustment. You add that with the desired replacement for everything accounting for the growth.

So we need to now go into the equations and understand how to account for growth. The rest is fairly straightforward. So we have the overall success rate here. Nothing to worry about. Then--

AUDIENCE: What are the desired phases, again? I'm sorry.

HAZHIR What are the desired phases?

RAHMANDAD:

AUDIENCE: Yeah, is it just--

HAZHIR

We should go into the equations. So they are a little bit more complex but very similar to what you see-- you just

RAHMANDAD:

saw. So let's first look at the replacement factor for growth. This is probably the more complex equation than the new equation.

So this is trying to account for what you need to adjust to get the growth that is needed. And the formulation for it is, for each of the stocks, for each of the stages, you have 1 plus the duration multiplied by the desired growth rate or the perceived desired growth rate.

So if my growth rate is 5% per year and that stage takes two years, that adds a 10%, 0.1, to 1 for expansion that comes from that stage. And then you multiply that for the expansion that comes from the next stage and the next stage and the final duration in the market stage.

So those expansion factors are the drivers of what the total expansion needs to be to get the desired replacement so that 10 years from now we have enough coming in. Now, the question is where did I get these numbers from, these formulations from?

So at the heart of that, it might be easier actually to look at one of these. Let me see which of these desired. So this one is easy. So sorry, the desired drugs is easy because it is the current value that you won't have. So desired P3 drugs is probably a good one to look at.

So desired P3 drugs is desired drugs divided protected duration in market. So this is the total desired rate of exit of drugs from the market. We divide that by the P3 success rate.

So this far, very similar to what you have already done. You're just expanding it to account for the success rate. You multiply that by the duration.

Now we get to the last part, which is the expansion for the growth for-- when this is going in, it needs to account for the extra that it needs to give in so that during the period of markets being-- drugs being in the market, protected duration in market, you grow it enough to get the outflow rate that you want.

This is where the formulation that Ross had comes in. So basically, the core idea is-- actually, maybe it is easier to do it in some. So we have the stock. Outflow, inflow. And the stock s .

What we want is that, this stock, we want it to grow with a growth rate of g . So ds/dt is gs , which is I minus O . Now this has I minus-- whoops.

So, yeah, OK. So we could write it in terms of s . So it would be s divided by τ .

And then if we turn i into some multiple of O . So let's say it is some kO equals I . That is, if k equals 1, we are in equilibrium.

A larger k then it becomes ks over τ minus s over τ equals gs . So s 's is cancel out.

So k -- so it could take 1 over τ out. k minus 1 equals g . Therefore, k equals $g\tau$ plus 1 .

So this is telling you what the inflow should be so that the stock can grow exponentially with the rate of g . So if your desired growth rate is g , the factor that goes into the inflow should be this factor.

AUDIENCE: But this requires that you assume that you can write down the outflow as some multiple. Or you can write down the inflow as some multiple of outflow.

HAZHIR Yes. And if it is a variable-- if it is a function-- so if k is a function of time, it could be k of time or k of s . But this

RAHMANDAD: way, you see that it actually doesn't depend on time or s or anything. And therefore, it becomes a nice constant that you can use, and it will give you an exponential growth in the stock.

Now, you didn't know that when you wrote the k . So this k could be a function of a lot of things. But the way it came out was that it is a simple thing.

AUDIENCE: Because it's a linear system--

HAZHIR Because it is linear-- because of the first-order differential equation solution that says if stock is growing

RAHMANDAD: exponentially, the net flow is also growing exponentially with the same rate. So that's really at the heart of why this formulation, this factor works out.

AUDIENCE: Does this also cover if the growth rate is exponential? If it is, then--

HAZHIR No, then the g will be changing over time because, as you grow, the fractional growth rate goes down. So if you

RAHMANDAD: make the g time variant and account for that, then it probably works. I haven't tested it explicitly, but I think it probably works. But then you have a moving g that accounts for it.

OK, so this is actually-- gives you a very simple solution to the problem of OK, what should be the inflow expansion factor to make the stock grow exponentially? Now I have created this inflow expansion factor. We can go back to the formulation.

So this is the inflow expansion factor for-- drugs in phase III is coming from the-- so this is the P2 success versus P3 success. Sorry. Yes.

OK, so now, going back to this desired P3, so desired P3. Now you can see, it is based on the desired inflow-- desired outflow being expanded to account for the next step's growth rate. That is, this term is saying, in the next step, you need to expand things by this much.

Therefore, the outflow of phase III should have that expansion built into it, which is the inflow of the next phase. And then you get that. You go backwards.

You go to the desired phase II. It starts with desired P3 drugs which already have this factor and then multiplies it by this factor for the phase III's duration. And then the next one does the same expansion for phase II and phase I.

So that's where the-- Alexander.

AUDIENCE: I was confused why you divide it by P3 duration, but now I see that that's the equilibrium.

HAZHIR Yes, that's to get to there.

RAHMANDAD:

AUDIENCE: Why do you need to multiply by the factor again here if you've already done it?

HAZHIR This is for the next-- this is for P3 duration. So the previous one was accounting, so let's go back to the P3.

RAHMANDAD:

So the P3 desired stock is looking at the P3 success rate. But a P3 success rate that allows drugs in market to grow with the desired factor, that is, to grow exponentially with the desired growth rate.

So for drugs in market to grow exponentially, you need 1 plus this protected duration in market multiplied by the growth rate. So rather than patent expiry, it should be really patent expiry expanded to account for that factor.

AUDIENCE: I didn't understand at all. I'm just confused why you're-- I was confused why-- because you necessarily need drugs in phase III to be growing [INAUDIBLE].

HAZHIR Yes. So once you want something to grow exponentially in this system, everything needs to grow exponentially in

RAHMANDAD: this system. Basically, because the net flow-- all of these net flows are growing exponentially with the same rate, same rate of growth for the stocks to be able to grow exponentially.

AUDIENCE: And why is that not accounted for when you had that growth factor in the desired P3 drugs?

HAZHIR So in the desired P3 drugs in here, I only accounted for what this P3 success should be compared to the patent

RAHMANDAD: expiry. Because this needs to be bigger than patent expiry for this guy to grow. And then I calculated based on that P3 success that results, what should be the stock of drugs in P3?

So that part was what you already had seen. In a lot of other formulations that you had, you had that calculation that you get the outflow P3 success, but the desired value of it. And I'm using the desired values based on the desired drugs in market, not the actual so that accounts for the other issue that we saw.

Similarly, for-- but then, when I get into desired P2, I need to get it based on P2 success and P2 success should account for the duration of phase III. So it now has the 1 plus phase III duration multiplied by the growth rate added to it so that the P2 success is larger enough, large-- is bigger than P3 success so that the drugs in P3 can grow exponentially.

AUDIENCE: Yeah, I guess I'm just confused. So right, this is all-- I guess I'm just confused as to why-- OK, so I get that you want the stocks to grow at a rate of g , the intermediate stocks. But I'm just confused.

And that's not a common for when you calculate desired P3 drugs? I get how you calculated it. But if--

HAZHIR So when I'm calculating desired P3 stocks, I didn't look at the P3 duration at all, that is, the adjustment-- the

RAHMANDAD: difference between P3 success and P2 success. So P3 success is going to be smaller than P2 success if we want drugs in P3, in phase III, to grow. That was not part of the calculation of the desired P3 drugs.

AUDIENCE: So then-- just out of curiosity, for the sake of understanding, what happens if you don't account for it in the desired phase II?

HAZHIR So basically, we underestimate the drugs in the pipeline in the phase II that are desired. In this model, it means

RAHMANDAD: the initialization will not be in equilibrium. And it also means if you have any out-of-equilibrium dynamics, it will not work. It wouldn't close the gap.

And in fact, it will create a steady-state problem if you do it that way because you're always lacking lagging in how many drugs you try to have in P2 stock or in P3 stock. So it will lead to a steady-state error in the growth rate.

So now you get these steps, how they are coming together. I actually have something that is not the best formulation here. And that is I'm using the patent expiry to drive the drug replacement with growth.

I could use the same thing that I used actually in the phase II drugs, which is the desired drugs p divided by protected duration in market. The difference in equilibrium is nothing because, in equilibrium, we're starting from the right value for the desired drugs p .

But if we start out of equilibrium, then this patent expiry at the beginning gives the wrong-- or kind of under- or overestimated replacement rate. So a better formulation here would be to use what we had there. Yes.

AUDIENCE: Makes sense.

HAZHIR So is the logic fairly clear now?

RAHMANDAD:

AUDIENCE: I know I was getting into--

HAZHIR No, no, it's good.

RAHMANDAD:

AUDIENCE: So when you're calculating the replacement factor for the patent expiry, why is it not just 1 plus g times drug development cycle. Why are you multiplying all the factors all together?

HAZHIR Very good question. Basically, if you write the-- if you try to do it that way, you just get the wrong answer

RAHMANDAD: because this is not a first-order delay.

So that would assume a first-order delay, From a start to the very end whereas this is a fourth-order delay. And therefore, the multiplication factor needs to break down to factors coming from each of those four steps coming together.

AUDIENCE: Which factors are you talking about?

HAZHIR So these are the factors you saw. For example, in the desired drug P3, you had 1 plus perceived growth rate or

RAHMANDAD: desired growth rate multiplied by projected duration in market. That's the projected duration in market. Then you have the P3 factor, P2 factor, and P1 factor.

We multiplied all those four with each other into this replacement factor for growth. So this weird-- this complex-looking formulation is just multiplication of those four factors. It was overwhelming when we saw it first.

But when you go through the steps, you see that each of them is fairly straightforward why you need that expansion factor. And so the way it works is basically it is saying, this P3 success needs to be the first or the last component bigger than the patent expiry.

P2 success to P3 success needs the next multiplier. P1 success, P2-- P2 success has the next component. And then P1 is start, so P1 success has the last one. So that's how these four come together to tell you how much you need to start at the beginning to get the right level at the end.

OK, so now you can simulate this model. And hopefully, I didn't break something.

AUDIENCE: [INAUDIBLE]?

HAZHIR So good question. So we have these stock adjustments that are very stochastic. And that is actually a good
RAHMANDAD: reassuring thing for me when I saw it because I know this means the numbers are very small.

So this is 10 to the power of minus 13. So it is basically saying, stock adjustment is 0. It's just numerical.

So that means, great, I have started from equilibrium without any need for adjusting anything. And in fact, all of the stock adjustments are basically 0. And now you can see that the drugs in market versus those in different phases are all growing exponentially.

But they are growing with the same rate. But because they are at different points, they look very different from each other. In fact, if you expand the growth rate and you can make it even much larger, the system will be-- this is 10% per month, which is a huge growth rate.

So they would look really different from each other. So drugs in phase III and drugs in market are now much smaller than the numbers you are seeing for phase I because of the delay. So a phase I-- so to get to these-- so here, we have drugs in the market that go up to 200,000-ish by the end.

To be able to get to 200,000-ish by the end, you need phase I-- or maybe looking at the flows are better because exploration because the time in the market-- I mean, doesn't make a big difference. So this one is in the hundred million range, partly because of the success rate.

But the bigger impact is actually, because of this fast growth rate, it is saying if you want to grow 10% a month 20 months from now, you actually need to start 10 times more or something-- I mean, you do the rule of 70, you can get a quick approximation of how much more you need to start. But that's the idea.

AUDIENCE: So general process question. How in the world should we have come up with this? I'm not saying that the question was like-- I could've done this for a year, and I probably wouldn't have done this, like--

HAZHIR Well, that's the point of this class. Next week, you can do it in one week.

RAHMANDAD:

AUDIENCE: How do you approach problems like this?

HAZHIR OK, so I'm designing things that definitely have new components for you. So almost no week, you come here and
RAHMANDAD: you say, OK, this was trivial, but it is not also something that you say, I have no idea even how to start. So the goal for me is to get you to think about things that you haven't thought about when you have been modeling in the past.

AUDIENCE: Well, I guess, I'm just asking in general, when you're-- and maybe this is a very broad question that this class is supposed to answer, but in general, when you're approaching these sorts of difficult modeling questions, how do you approach them? Again, maybe this is so big it's not meaningful. But what's your problem--

HAZHIR Yeah, so actually, a lot of these-- this one, I had never solved it before. So when I yesterday started, I said, OK, let
RAHMANDAD: me actually think about it so that, when I come to the class, I'm not going to be looking at it and say, oh, shit, I haven't thought about this part of it.

So that was my starting point. And when I went into it, I said, OK, this growth thing is not trivial. I have asked you to do something that I have not done myself. So let me actually write it down.

And I had to actually create that, so the analytical thing that I showed you, to get to the point of-- and I started-- so let me tell you my process. So I started and said, OK, this is easy. You start with some inflow. Start, you multiply that with the time constant, and you get to the desired value for each stock.

And then I was going towards the end, and I said, oh, I don't have the inflow. I'll get the simultaneous equation error. So I have to drive the equilibrium from backwards.

So I drove the equilibrium from backwards. And I said let me stop, not worry about growth. I first solved the problem without growth.

Then I said, OK, now I need to think very clearly about growth. Let me solve the growth problem without having multiple phases. Let me just solve the growth problem for the market condition where things go directly into the market.

So I wrote down that equation, solved it, and said, OK, now I have a growth factor that comes in. Then the rest falls in place. It's kind of-- was relatively straightforward.

And of course, I was doing testing all the time. So without growth, I needed to be in equilibrium. And things adjust fast, and then it grows. So anyway, that's the mental model.

Now, this is doing OK. We don't know whether it will oscillate or do weird things, so we could test those as well. So for example, if I change the desired revenue to do something other than exponential growth, so--

AUDIENCE: Try the line.

HAZHIR Try what?

RAHMANDAD:

AUDIENCE: The ramp.

HAZHIR Yeah, we could even do the ramp. But let's do the step change because it's easier to get started with. So, I don't
RAHMANDAD: know, 250.

So right now, this is getting things out of equilibrium because my desired growth rate is 10% whereas the actual desired growth rate is 0. So I need to fix this one as well. So that just needs a little bit of fixing so that they are consistent internally with each other. Otherwise, the system learns the actual growth rate and the perceived desire growth goes down, but it takes so long that it creates a lot of hectic dynamics.

OK, so now we have the desired growth rate. You see that the drugs in the market take a while. In fact, in 100 months, they don't get there because the drug development process is that long.

But they are moving in the right level. That is, if you look at the revenue versus desired revenue-- so where is the revenues? They are-- no, they are not moving in the right-- ah, interesting because I have created a perceived growth rate that is nonzero. You see?

So the perceived growth rate, the signal from that step function to the system is that, wow, there is huge growth rate, and now it is adjusting everything towards that huge growth rate. So actually, I have to also fix this guy if we want to see--

AUDIENCE: What is the role of the perceived growth rate even in the growth sector? Why don't we just-- because this is--

HAZHIR It doesn't have a big role. I could easily just use the desired growth rate to drive it. It is just taking a little bit of an
RAHMANDAD: adjustment so that growth rate is perceived rather than the real. It's very easy to drop that and perhaps better in this case. Good point.

But that was a good test case for it doesn't work. So in this case, if I make it a constant with a slider and have its base value at 0, then things should work better for desired versus actual revenue. Yeah, but it is going now very slowly because it is not getting the signal of the growth.

It is just very slowly adjusting towards it. And this is 100 months, so I should probably simulate it for longer to see meaningful impacts. Let me reset these-- no.

So now let's do something that changes the growth rate from 0 to-- so maybe it starts at 3%. Did I do this step? No, I didn't.

So I want the growth rate to be positive and then becomes smaller, not as big. So it goes through a step change. It starts from, let's say, 2% per month to 1% per month at time 50 or something like that.

So the desired growth rate is now changing in a step function. What you can see is that the P1 start rate goes down but doesn't go to 0. So the max zero constraint doesn't kick in.

And then drugs in the market-- or we can take a look at the revenue, see how well the revenue works in this case. And again, remember that the perceived desire. So if we make this perception time faster-- we could even make it very fast-- then the adjustment becomes faster so you don't have the long adjustment period because you don't measure the--

AUDIENCE: You're hitting the--

HAZHIR Yes, and now I'm hitting the max, so that will create some steady state-- not a steady state, but it will create
RAHMANDAD: some additional. Yes. What's that? Oh, so, here, in the P1 start, now I just can't get rid of these drugs because we don't have cancellation. If we add cancellation, we don't need to worry about this.

So perhaps we could change this guy to go to 0 point I don't know 13. Yeah, so now it wouldn't hit 0 I think. Yeah, it just goes to 0. So now let's see what's happening with the desired revenue.

So I'm now doing tests that I haven't done myself. So there is still some steady-state difference. And I think if we simulate it for longer, that should go away. But let's see if I have x final time. Always put the final time on your model screen.

So let's see.

Because we have 2% and then 13 or something like that. Yeah. And then or maybe 15, I'm not sure.

And then we said, this guy. Let's make it very small so that we quickly adjust. Yeah, this is kind of doing fine.

And then we can go to 500 or something. So we see the full range. What happened?

AUDIENCE: Did you mean to make [INAUDIBLE] to go down or to go up?

HAZHIR Huh? I wanted the desired growth rate-- well, I didn't mind going down. But somehow something weird happened
RAHMANDAD: here that I don't know what it is. No, nothing weird is happening. It's doing what it is doing.

So desired revenue and revenue. Let's see if it can catch up. Yeah, you can see that it does catch up.

Now, here I'm doing the change at time 10. That's too early, so let's do it at time 100 so that you have a longer period of the faster growth. You still get the behaviors to match.

In fact, even if you went into a no-growth process, which we can test. So we go to minus 0.01. For a while, it wouldn't do well because of the-- because of-- yeah, that's a long while that it doesn't do well.

AUDIENCE: Why is it?

HAZHIR So the reason is that now you have a lot of revenue, and you can't get rid of this pipeline. And it takes--
RAHMANDAD:

AUDIENCE: --time for it to process.

HAZHIR Yes, basically, a long time to get rid of all the things that you had-- you already was expecting these huge growth
RAHMANDAD: rates you were pumping into the pipeline. And now, without cancellation, so this shows basically the importance of cancellation in the conditions when things are going down.

AUDIENCE: So the time between those two peaks should be about the total time, the total duration from start.

HAZHIR Not to start to finish-- eh, it's harder to say because, as soon as you see that the perceived desired growth is
RAHMANDAD: going down and that is happening relatively quickly, now, you will stop investing. But stopping investing means 0. So now it is 0. You see, all the way to the end, it has remained 0. It just can't do anything more than this.

And with that 0 rate, it still cannot match the desired stock. So when that peaks, so that is your revenue. It is when your drugs in the market peaks.

And the drugs in the market peak when the inflow starts to go below outflow. That depends on the length of these three first step delays, not the last one. So it is more about the length of those delays rather than the last step.

AUDIENCE: [INAUDIBLE] problem with the third question is I almost feel like perceived desired growth rate in the real world should be not a function of a exogenous desired growth rate, but a function of exogenous desired revenue.

HAZHIR Yes, it should be based on desired revenue. So we could get it from the desired revenue directly. Yeah,
RAHMANDAD: absolutely. We could get it just directly from the desired revenue.

I don't remember whether I-- actually, I might actually have it. Actually, the perceived-- yeah, it's the same numbers that we have. So it is converging to the right numbers. But you could get it from the trend of the desired revenue.

So anyway, I'll share this model. For next week, we have our old friend Mr. Ponzi joining us. So some of you are familiar with the Ponzi model. Some of you are not.

So Ponzi is this guy, Charles Ponzi. In the early 20th century in Boston, he made a claim that I can give you great returns on your investments because I found this loophole in some bullshit story, basically, that you can buy these stamps here and sell them in Spain for 10 times the price or something like that. And I'll give you a 50% return on your investment over a 45-day period.

And people, of course, were skeptical at the beginning, but he started paying those who came back after 45 days the promised return. So more and more people joined. In a few months, almost half of the Boston was investing with Mr. Ponzi.

It grew exponentially, and then it crashed. And what he was doing was basically getting money from this group that are investing and paying to the group that are coming back to get their investments. That was the mechanism.

So the task is to build a model of the story of Ponzi. In some ways, it is easier than some of the previous tasks because it is not a very complex story, but it-- and it doesn't have very strange or technically complex formulations, but it does require you to actually bring different pieces together.

So you need a financial sector. You need to account for actual money versus what he has promised. These two are not the same.

And that's very important because you run out of actual money. That's when basically you go bankrupt and people-- whereas what you have promised is what you are paying based on. So that's important.

You need to somehow account for trust in the system one way or another. Now you should decide. So there is a lot more flexibility in how you model Ponzi's story.

So the problem statement that is in the folder has the basic story of Ponzi in one paragraph. There is link to Wikipedia page. Read that. That gives you a little bit more background. That's five minutes of reading so that you are grounded in the core story.

But don't forget the desire to build something that is a little bit more generic. That is, you can think about Social Security to be a Ponzi scheme in the sense that each generation is paying the previous generation's retirement, Social Security benefits. As long as there is enough inflow to replace that, things work out fine.

So Ponzi schemes are not generally neither illegal fully as long as you are clear what you are doing. So if he told people that I'm getting money from one to pay to the other, it would've been legal, but then he wouldn't have any money-- any investors. And you can change them in a way that it kind of works.

Madoff, the other big Ponzi schemer of the 21st century and late 20th century, he's as famous. He passed away in prison just a couple of years ago, but he actually scammed a lot more, many billions of dollars. And there are many other Ponzi-type stories around us. And there is the whole history of dozens of interesting cases.

OK, so that's the plan for the coming session. Hopefully, it would be a fun model. Make sure you have a model that follows all the basics, but also creates the growth and collapse history of Mr. Ponzi's scam with reasonable empirical ranges for parameters and so on, without getting bogged down into parameterization. Yes.

AUDIENCE: You're assuming that there's actually no investment happening. [INAUDIBLE] no growth [INAUDIBLE].

HAZHIR See what you want to do. You can have a real investment happening with a real rate of return that Mr. Ponzi's
RAHMANDAD: privy to but others are not seeing. And that's what Madoff did.

He did invest, but he promised more than what he was actually delivering. So for a generic model-- or Social Security does invest the money. There is a return.

So a generic model that is more generalizable would have that. But if you're short of time, that wouldn't be my first priority. So you can decide what you want to prioritize on that.

I think we're out of time, so let's be done with it. For those interested, I'm just going to show you one last thing, and you can take off if you want. But with the current AI stuff, there are good things you can do with model documentation and parameterization.

So with the pharma model, just to let you know, I turned it into text in Vensim-- I didn't do anything. It's just you do this in Vensim. So you can get this text of the model. I sent it to Cloud AI and told it please document my model.

Basically, it provided comments for every equation. So the comments you will see in this pharma model are not by my hand. They are all cloud commenting, the model, and it does a decent job. That is, it understands what the equation is doing. It provides meaningful explanation.

Now, that is pretty impressive. What is magical is that I told it, in another prompt and discussion, OK, this is a model of pharma industry. Please go and find the parameters from the literature and ranges for those parameters. Put them into a table with citations, and then insert them into the model. And it did that as well.

So now you can look at this model, and you will see that, every equation, every parameter has a detailed explanation with a bunch of citations. And I checked a few of them. They are not all fully correct, but they are all in the reasonable ranges.

That is, so these are the citations in this-- you will see. It has taken numbers from the paper, but sometimes not the best number, sometimes a number that is-- for example, there are lots of these papers that look at drug success rates that are looking at different categories. So it has not always found the right category.

Rather than the biggest category, sometimes it has anchored to a subset of drugs, things like that, which-- so always go and check the ultimate source. But this thing would've been something I would never do it for a class like this, but now it takes me 10 minutes to do it, so why not? So OK, go have fun.

AUDIENCE: You're saying, in two years, we won't even have to learn how to build these models.

HAZHIR I don't know. So I think there is always-- not always, up to some point that these AIs can do all of the modeling.

RAHMANDAD: You can become much more productive with getting help from AI.

There is a point, who knows when in the future, where you can't actually add much value beyond telling AI what model you want and how to calibrate it and so on. We are not still there. I don't expect it to be in the next four, five years, but because things are growing so fast, I have no idea whether that thing is coming soon or not.

In a way, modeling is one of the most complex human things because you have to make so many assumptions about what is important, what is not important. That's what our brains are still fairly good at compared to many of the AIs. So the point that this task becomes completely automatable, I don't know what competitive advantage we have on the cognitive task, but that's a conversation for a beer rather than end of the class.