Case study: The Race to Develop Human Insulin

What were the optimal actions for the competitors at different stages?

https://play.library.utoronto.ca/watch/2aaafb83a36ee32e17689cecc9f2bb0b

Introduction

In 1976, Eli Lilly & Co. held a symposium expressing their concern about the decreasing supply of animal pancreas, which was once the most important source of insulin for treating diabetes. In the 1970s, insulin demand increased, but animal pancreas supply decreased rapidly on the market, and 10% of patients were allergic to animal insulin. Thus, Eli Lilly & Co. expressed interest in manufacturing synthetic human insulin using recombinant DNA technology.

Three professional teams “accepted this challenge”. They were Genentech, the University of California-San Francisco (UCSF) and Harvard. Genentech’s first project after its founding was the somatostatin gene project, which they thought would be very helpful for the synthetic human insulin project. The UCSF laboratory was at the forefront of recombinant DNA techniques, which was a necessary technology to output synthetic human insulin. The Harvard Biological Laboratories had worked out the technique of crucial gene identification and they were interested in manufacturing synthetic human insulin. In a word, all three teams were enthusiastic and confident about the research of synthetic human insulin. Genentech decided to start the research by synthesizing somatostatin. On the other hand, the UCSF laboratory and the Harvard laboratory both chose to begin with developing rat insulin. Generally, after they set up the plans, there would be four sequential steps for their research of synthetic human insulin: isolation, conversion, cloning and expression.

Although they were all brilliant laboratories, only one team would first get the result and win the race of research. This type of race is called the Research & Development (R&D) race. Unlike normal operational activities, people usually do not expect a short-term profit from the projects. Instead, these projects work for the organization's long-term benefit such as patents and copyrights. In this case, the winner would not only be remembered as the inventor of the synthetic human insulin but would also win cooperative opportunities with Eli Lilly and they could apply for patents and copyrights for further profit. The laboratories needed to apply the most suitable strategy for each stage and to track the progress of their competitors. Based on the competitors' progress, one laboratory might want to spend different efforts on the current step either to work more quickly to improve the probability of winning or to reduce the potential losses such as the extra time and money inputted.

In this paper, we would like to find the optimal strategy for each team in different stages. We are interested in how much each team should have expected to win and how much they should have input in each stage. After we get the framework, we can also apply the same methods to many other R&D cases.

Assumptions

Since the two university teams were using similar approaches, we treated them as a group, we called them "the universities". To simplify the calculation, we also combined stages cloning and expression because we had limited information on the detailed situations at these two stages. Based on these assumptions, we could perform a 2-competitor and 3-stage R&D analysis. The total profit would be calculated as the present value of the winning prize in 1978 when the actual race ended. Notice that Eil Lilly instead of Genentech would be responsible for producing human insulin because they had signed an agreement with Genentech. Thus, we supposed that Genentech would “sell the patent” to Eil Lilly. We assumed that Eil Lilly would provide resources and finances that had the same present value as the “patent” for Genentech’s future research as a return. The value would be considered as the potential benefit of winning.

Based on the historical discount rates of the U.S., we used an 8% per annum discount rate and assumed that it was constant through the years. Because we had limited information on how much each team had input into the research, we assumed that they would simply earn 0 if they lose the race, that is, they would not lose their inputs. This somehow makes sense because their research might still be helpful for their future studies.

Methods & Analysis

We used the R&D race model to solve for the optimal strategy of each team at a given stage. The R&D model focuses on deriving instantaneous probabilities over a small time interval. At each stage, we evaluated the probability that a team had exactly one success in a time interval as the team could move on to the next stage only if they got one success. With the instantaneous probabilities, we could estimate the instantaneous value of winning for each team, that is, how much the teams could value the winning at the current stage.

To analyze an R&D race that contained multiple stages, we would like to calculate the value of winning for each competitor and the probability of winning at the current stage. We noticed in the Epilogue that "on October 14, 1980, some $1.1 million shares of Genentech (the actual winner), at a price of $35 per share,...by the end of the day it had settled down to $71.25". (Barese, 1991) It showed that the market value of the winner had improved ($71.25 - $35) ×$1.1 million ≈ $40 million in 1980. In addition, a more direct income would come from Eli Lilly. Barese pointed out that Eli Lilly held 80~85% of the insulin market in the U.S.. Based on the fact that the annual total sale of insulin was about $200 million, we approximated that Eil Lilly would make about 85%×$200 million = $170 million per year by the sales of insulin in the mid-1970s. The percentage makes sense because Eli Lilly might achieve more market power after achieving the technology of synthetic human insulin after the race. These two profits would be the main prize for the winner of the race. Therefore, we could calculate the present value of the total profit in 1978, which was the actual ending year of the race. With an 8% interest rate and the corresponding issued years (1980 & 1975) of two profits, we knew that the present value of the prize in 1978 would be $34.29 + $214.15 = $248.44 million.

Then we would like to compare the quality of the laboratories, that is, to set each competitor a parameter λ that represents the competence/efficiency of the team. Based on the case description, we could suppose that Genentech and the universities had similar levels of competence. On one hand, Genentech was working on a similar project, which provided valuable experience for the human insulin challenge. On the other hand, the universities had famous biologists and scientists leading their teams, and they also had related experience. It means that the two competitors were equally competent. However, due to their different choices of approach, we could see from the case description that the universities faced more barriers including the lack of materials and facilities. For example, Harvard's request of building a P3 facility had been declined by the community, and thus, they could not do their research on time. UCSF did not get the insulinoma promised by Brigham Hospital, and thus, they needed to spend more time and money on surgical removal of the mouse pancreases. Moreover, UCSF's P4 facility issue in 1978 had directly caused their loss of the race. In contrast, Genentech never had these problems in their research because their approach did not require such high level facilities or materials. Since there was more ambiguity in the universities' approach, we assumed $\lambda = 2$ for Genentech, and we set $\lambda = 1$ for the universities as a penalty of the complexity that had reduced their research speed.

After we have got the value of the final prize, the value of losing, the interest rate, and the parameters of competence. We could then input these values into the calculation system in the excel worksheet provided by Professor Ajaz Hussain. The worksheet would output the intensity levels of the groups and their valuation of the current winning at different stages. The intensity level at the current stage represents the effort input at the current stage of the research. Generally, when a team sets an intensity level α, their cost of the input at this stage will be around $\$\alpha^2$. The intensity level depends on the opponents' progress. For instance, if one team is about to finish their research, while the other team is only halfway through, then the latter may reduce their expected value of winning their current stage because they will probably lose the race even if they put in much more effort than before. Therefore, the system would first fit the given parameters that we had got to the model of the instantaneous value of winning for each team to solve for the intensity level that maximizes their benefit.

The instantaneous value of winning for a team (say, Genentech) between a given time period (between t and $t + dt$) depends on the probability that one team finishes the research before the other at the current stage. In our case, there were three components in the expression of instantaneous value:

1. the value of winning in the current stage for Genentech when it moved to the current stage, whereas its opponent, the universities stayed at the previous stage;
2. the value of winning in the current stage for Genentech when it stayed at the previous stage, whereas the universities had moved forward to the current stage, and;
3. the cost of input for Genentech in whichever situation.

For the first component, we needed to calculate the probability that the team was one step quicker than their opponent, and then multiply it by the value of winning in the current stage. For example, the probability that Genentech was quicker than the universities could be expressed as $x_u e^{(-\lambda_g x_g t)} e^{(-\lambda_u x_u t)}$, where x_g and x_u were the intensity levels of Genentech and the universities correspondingly, t was the time needed for the success at the current step, and we set $t = 1$ year in the calculation. The $e^{(-\lambda_g x_g t)} e^{(-\lambda_u x_u t)}$ part represents the probability that neither team would succeed in one year at the current stage. Then we multiplied it by $x_g \lambda_g dt$, where $\lambda_g = 2$, $dt = 1$, and we got the first component for Genentech. We could also get the probability that the universities was quicker than Genentech, that is, the second component by using the same method. We then multiplied the first two components to Genentech's expected value of the current winning V_g in the corresponding situation. The third component could be expressed by the probability that either team would win in the current stage multiplied by the total cost that Genentech had spent at the current stage. Since we had also set an 8% discount rate, by combining the three components and the discount rate, we achieved the expression of the instantaneous value of winning in a given stage for Genentech:

$$V_g(m,n) = \int_0^{\infty} e^{-0.08}[2x_g e^{-2x_g} e^{-1x_u} V_g(m+1,n) + 1x_u e^{-2x_g} e^{-1x_u} V_g(m,n+1) - e^{-(2x_g+1x_u)} x_g^{\,2}]dt \ ,$$

and similar for the universities, we got:

$$V_u(m,n) = \int_0^{\infty} e^{-0.08}[1x_u e^{-2x_g} e^{-1x_u} V_u(m+1,n) + 2x_g e^{-2x_g} e^{-1x_u} V_u(m,n+1) - e^{-(2x_g+1x_u)} x_u^{\,2}]dt \ .$$

We could also use online calculator to solve for the value of the intensity levels (x's) that satisfied the FOC of both equations above, and express it as a reaction expression, which specifies how the team would react rationally given the opponents' actions at the current stage. For Genentech, we had:

$$x_g = (-\,1x_u + \sqrt{(-\,1x_u)^2 + 1x_u[V_g(m+1,n) + V_g(m,n+1)]})/2 \ ,$$

and similar for the universities, we had:

$$x_u = (-\,2x_g + \sqrt{(2x_g)^2 + 2x_g[V_u(m,n+1) + V_u(m+1,n)]})/1 \ .$$

The excel worksheet would then help us find the exact values of these expressions in different situations.

Results

The excel worksheet returned the teams' valuation of winning (V) in the current stage, and the corresponding intensity level (x).

Value of current stage		The universities					
		1		2		3	
Genentech	1	177.38	48.61	111.11	117.58	38.59	193.67
	2	216.03	16.17	175.77	61.37	90.88	149.64
	3	234.62	3.11	223.08	81.05	163.21	81.05

Table.1 The value of winning in the current stage

Intensity at current stage		The universities					
		1		2		3	
Genentech	1	1.49	1.49	0.95	1.56	0.34	0.85
	2	1.56	0.95	1.79	1.79	1.25	1.90
	3	0.85	0.34	1.90	1.25	3.33	3.33

Table.2 The intensity level at current stage

For example, for a winning prize, which was worth $284.44 million in 1978, if Genentech had succeeded in the second stage, whereas the universities did not finish in the second stage, then the winning of the second stage would be worth $216.03 million to Genentech, and Genentech would set their intensity level at 1.56 for the third stage. On the other hand, winning the second stage would be worth only $16.17 million to the universities because they had a high probability to lose, and their approaches were also less efficient than Genentech's as mentioned. Thus, the universities would only set a 0.95 intensity level to minimize their cost in further steps. If the two competitors both finished the second stage at the same time, then they would both apply a 1.79 intensity level because they were equally likely to win. In this case, we noticed that the teams' valuation of current winning were different considering the competency of each other. However, their intensity levels were the same here because it turned out that they were able to finish the current stage at the same time though they had different competence. Hence, the competence seemed to be unimportant to the probability of winning in this case. In addition, the intensity level never dropped to 0 because the probability of winning never dropped to 0, and scientists would not easily give up in the middle.

We could also apply the estimation with more case details. For example, we had seen that Harvard faced political issues regarding the possession of a P3-level lab at the first stage between 1976 and 1977. Meanwhile, both UCSF and Genentech had been at least one stage (one step in the simplified case) ahead of Harvard. At this time, Harvard faced a situation (1, 2). Because Harvard got held up, they reduced their expected value of the first stage, and their focus at the first stage would be to slow down and to avoid too much cost. They could drop the intensity level to 0.95 for competing in the second stage. If Harvard was lucky enough to catch up with the other teams at the second stage, they then got to a situation (2, 2), then they could increase their intensity level to 1.79 for the third stage because both their probabilities of winning in the third stage as well as the final race had increased. In contrast, if Harvard was stuck at the first stage for a long time, and the situation turned into (1, 3), then they could lower their intensity again to 0.34 because their probability of winning had been much lower.

Besides, we had noticed that the teams had symmetric optimal intensity levels. For instance, Genentech's intensity level at (3, 2) equaled the universities' intensive level at (2, 3), whereas the model suggested different reactions based on different levels of competence. In general, the model suggested that Genentech would spend less time (or money) on the research than the universities given the same intensity level. For example, Genentech would spend $27.46 million for winning the final prize when both teams were at the final stage (3, 3), but the universities would have to spend $34.75 million to win. Note that the spending could contain the value of different types of effort, such as money and time. Since we had assumed the universities to be less efficient than Genentech according to their approaches, we were also assuming that the universities would require more resources and effort to win in a stage with a given intensity level. It makes sense because the universities' approach in practice did require more resources than Genentech's approach according to the actual case. Thus, these results satisfied our assumptions.

Conclusion

In conclusion, we had summarized the optimal actions for the competitors. For the universities, these actions could increase their chances of winning and avoid too much cost. For Genentech, these actions could also help them win with a lower expense. The same model can be used on similar R&D cases. However, like this case, there will always be ambiguity in real life, and thus, the output will not be completely reliable. Researchers will still need to make their decisions to control their development.

Limitations

Since we had simplified the race by combining the two university teams and reducing the stage, the estimation was biased. The assumption of the expected value of losing was also inaccurate. It should be greater than 0 because there would at least be some sunk cost. Also, as mentioned, there always existed ambiguity in the progress. Although we had considered some ambiguity, we did not discuss it in detail. In addition, we did not consider the effect of information such as the reports of the other teams' progress. This could also cause a different valuation and intensity.

Reference

Barese, Paul. *The Race to Develop Human Insulin*. Harvard Business School, 1991.

Hussain, Ajaz. *Ajaz_ECO_404_FALL_2022_R_and_D_race.* Microsoft Excel, 2022.

Appendix

Genentech				
Stage(G, U)	Intensity	Reaction($)	Expected value of current stage($)	Expected value of final winning($)
(3,3)	3.33	27.46	163.21	248.44
(3,2)	1.90	10.61	223.03	248.44
(3,1)	0.85	5.14	234.62	248.44
(2,3)	1.25	17.00	90.88	163.21
(2,2)	1.79	15.05	175.77	223.03
(2,1)	1.56	8.14	216.03	234.62
(1,3)	0.34	8.74	38.59	90.88
(1,2)	0.95	14.31	111.11	175.77
(1,1)	1.49	12.41	177.38	216.03

Table.3 The aggregated strategies for Genentech

The universities				
Stage(G, U)	Intensity	Reaction($)	Expected value of current stage($)	Expected value of final winning($)
(3,3)	3.33	34.75	81.05	248.44
(3,2)	1.25	14.26	19.05	81.05
(3,1)	0.34	4.37	3.11	19.50
(2,3)	1.90	18.53	149.64	248.44
(2,2)	1.79	18.52	61.37	149.64
(2,1)	0.95	10.83	16.17	61.37
(1,3)	0.85	8.64	193.67	248.44
(1,2)	1.56	1.56	117.58	193.67
(1,1)	1.49	1.49	48.61	117.58

Table.4 The aggregated strategies for the universities

Parameters	input value
1st Prize(win)	248.44
2nd Prize(lose)	0
interest rate	0.08
λ_g	2
λ_u	1

Table.5 The parameters based on assumptions