Application Portfolio – EDS 71
New Techniques in Drug Discovery

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Abstract

The following report examines the financial development of a manufacturing system that produces a disposable sensor system for use in drug discovery. This new product replaces many current sensor dye packages used for high throughput drug screening by pharmaceutical companies. The parameters of the drug discovery sensor system are outlined at the beginning of this report to develop approximate system parameters. The later sections use several analysis techniques to predict manufacturing performance in uncertain demand markets. The analysis techniques employed include 2-stage decision analysis, binomial lattice, and option lattice models. All analysis techniques show clear advantages to a flexible manufacturing infrastructure that allows for plants to be easily opened or shut down, essentially having options **on** the system. Analysis shows that it is beneficial in uncertain markets to have many smaller plants than one or two high capacity plants.

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Part 1: Defining the Topic – Drug Discovery System Overview

A description of the system

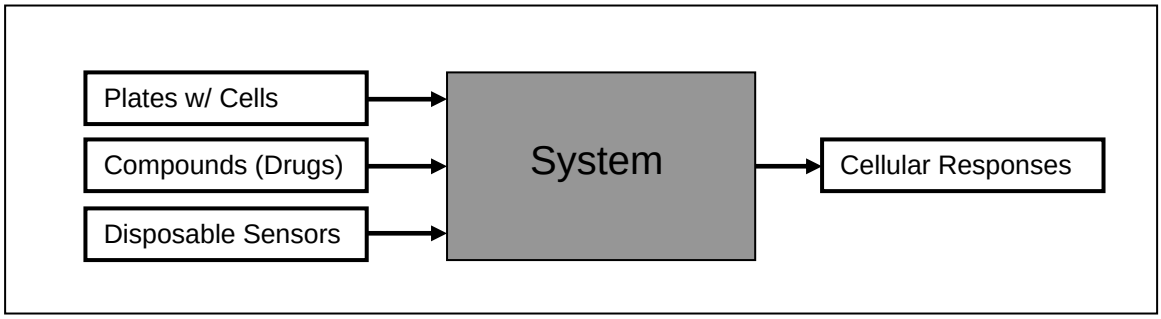
The system proposed for this application portfolio is a new type of automated drug screening machine. Currently, large pharmaceutical companied spend on the order of 100 Million dollars to bring a single drug to market. A large percentage of this effort goes into the initial Hit/Miss high throughput assays followed by required toxicity screening once a desired compound has been found. The majority of these pharmaceutical companies, such as Wythe, Pfizer, etc, use a single machine called a FLIPR developed by Molecular Devices, to conduct their high throughput screening processes. The initial capital cost for a single FLIPR is around $500,000 depending on the options. There are also a number of "disposables" used by the machine during the screening process, which increase the cost per screen. Often, many of these machines are used in parallel to screen thousands of compounds a day.

The system that will be examined is a new type of high throughput screening assay, which far exceeds the current FLIPR system in terms of quantitative data obtained during the screening process. The FLIPR can only process a single type of cellular activity, such as intracellular calcium levels. When drugs are screened, the FLIPR detects which compounds produce changes in intracellular calcium levels that exceed a pre-determined Hit/Miss threshold. This "single sensor" system is limiting and causes a large number of false positives and negatives. The new system uses an array or multiple types of sensors to create a detailed, high content, map of cellular response in the presence of a certain compound (drug). This higher content screening system is capable of screening more "families" of drugs while also reducing the percentage of false positives and negatives.

The physical design of the new system has yet to be determined, but the technology used to screen the assays has been proven and the design parameters can be determined

A discussion of the major design parameters and issues

There are a whole series of design parameters that have yet to be determined due to lack of knowledge about the market demand and customer preferences. A minimal system would will require the machine to feed in a standard 96 well plate containing cells, inject the compound (drug), and then measure response using a series of optical sensors. This alone requires three separate systems to interact in a closed "black box" environment that will output cellular responses. This can be seen in the following flow diagram:



This system would still require sophisticated robotics, liquid handling, optics, and data processing. Each system has unique design parameters that will be primarily market driven; however, an initial table has been created to outline the basic design parameters of the system independent of market variables (i.e. purely functional design parameters):

Robotics	Liquid Handling	Optics
transport plates into machine	various compound dilutions	fast (read times < 1 second)
low plate accelerations	pipette tip disposal	low background noise
no dust contamination	rinsing	several ex/em wavelengths
accurate positioning (± .5 mm)	waste liquid disposal	reliable sensor interaction
multiple feed lines	robust pumps	
plate removal / disposal	no cross contamination	
sensor placement on plates		

An outline of the major uncertainties about the performance of this system

- Competition with FLIPR and Patch Clamp technologies (Customers will be unwilling to switch products)
- Possible uses of the system other than drug screening (toxicity studies, cell growth, cell metabolism, etc). This will greatly effect total demand
- Degree of automation (possible demand for automated cell culture included within the system)
- Maintenance costs
- Future trends in drug screening
- Future unknown competition
- Number of sensor consumables used by the average customer (run costs)
- Environmental restrictions on sensor waste material

Part 2: Defining the Salient Uncertainties

Uncertainly # 1: Market Demand

One of the largest sources of uncertainty in the design of this drug discovery system is the total market demand after its release. There are several design criteria that will depend on the size and properties of the market. Some of these criteria include degree of automation, overall system complexity, and component selection. If the market is expected to be large, then high capacity manufacturing facilities will need to be constructed. In the system needs to be designed to allow for high speed automated manufacturing, which will result in increasing returns to scale.

Also included in the market demand aspect of this project is the breadth of uses for the system. Is this system going to be used strictly for drug discovery? Or will it be used in other applications such as long term cell growth studies? This will affect the degree of modularity and flexibility embedded in the system design. Certain customers may only want a specific part of the system.

There are several measures that could be used to characterize the future market for this system. It would be impossible to characterize every aspect of such an uncertain market, but there are several key parameters that could be used to approximate a model. First, the market needs to be broken down into all sections that will use this system for different applications. From each market could be quantified by current size, expansion rate, and uncertainty in each of these. The following table is an initial blank Metric for market parameters:

Markets	Market Size	Size Uncertainly (STDV)	Growth Rate	Growth Rate Uncertainty (STDV)
High Throughput Drug Discovery	?	?	?	?
General Cell Studies	?	?	?	?
Unknown	?	?	?	?

Table 1: Initial Market Classification Metric

It is also possible that each one of the individual markets listed above has their own preference for what type of system they would prefer. A larger, high throughput, company will most likely prefer expensive fully automated systems, while a smaller research lab may wish to have a less expensive, simple, low throughput device. To simplify this project, each of the above markets will be given a type classification. In general, the large high throughput companies are those interested in drug discovery and toxicity screening. By contrast, it is often the smaller research laborites that perform cell grown and classification studies. If there ends up being large demands from both areas, then perhaps a modular system design would be advantageous. This way, both large and small customers could purchase a product well suited for their use.

Uncertainty # 2: Manufacturing Costs

In addition to market demand characteristics, manufacturing costs are a large uncertainty with this system. To streamline this financial analysis, the system will be split into two subsystems. Product line 1 will be a simple disposable sensor platform that will replace existing indicator dyes. This platform could be used with many of the current fluorescence measuring machines. Product line 2 will be an expensive automated platform to replace the FLIPR produced by molecular devices. This platform will use the sensor system (Product 1) instead of traditional indicator dyes used by the FLIPR. For each of these systems, production and capital costs need to be estimated to develop a financial model.

Each of these models will require plants with different properties. The disposable sensor factories will not require large facilities with many factory workers. However, it will require large energy inputs to run the injection molders. A large percentage of manufacturing costs will be coupled to energy prices and their future fluctuations.

The manufacturing of the automated platform will depend on less on energy costs, and more on labor costs. Each machine will require more human labor to assemble, package, and ship, than the disposable sensors. The manufacturing costs will be strongly coupled to labor costs, which are uncertain.

Parameter Estimation and Sources

Market Demand

It is extremely difficult to estimate many of the parameters in the above matrices accurately. To get a close approximation of each markets properties, the companies that supply many of the existing products to these customers were examined.

The primary supplier of high throughput drug screening platforms is Molecular Devices. There website can be found at: http://www.moleculardevices.com/. There are other companies that produce equipment for drug screening applications, but Molecular Devices is the primary (90%) supplier for high throughput drug screening. A corporate representative for Molecular Devices estimated that approximately 25-35% of molecular devices revenue comes from their high throughput drug discovery platforms (FLIPR). As an initial market estimate, the target market demand for this new drug discovery system will be modeled to follow molecular devices revenues over the last 10-15 years. The following plot is the companies' financial history over the last four years.

Company Financials

Molecular Devices

MDCC
Molecular Devices Corporation NASDAQ-NM Learn More About XBRL

Income Statements | Balance Sheets | Statements of Cash Flow | Financial Ratios

Annual Income Statement (values in 000's) Get Quarterly Data

Period Ending:	12/31/2004	12/31/2003	12/31/2002	12/31/2001
Total Revenue	$148,529	$115,581	$102,157	$92,231
Cost of Revenue	$56,274	$43,256	$40,561	$35,538
Gross Profit	$92,255	$72,325	$61,596	$56,693
Operating Expenses				
Research and Development	$22,038	$18,679	$18,002	$27,730
Sales, General and Admin.	$52,469	$43,457	$35,435	$33,381
Non-Recurring Items	$6,157	$0	$0	$0
Operating Income	$11,591	$10,189	$8,159	($4,418)
Add'l income/expense items	$18,607	$872	$1,562	$3,806
Earnings Before Interest and Tax	$30,198	$11,061	$9,721	($612)
Interest Expense	$187	$0	$0	$0
Earnings Before Tax	$30,011	$11,061	$9,721	($612)
Income Tax	$12,778	$3,319	$2,916	$4,625
Net Income-Cont. Operations	$17,233	$7,742	$6,805	($5,237)
Net Income	$17,233	$7,742	$6,805	($5,237)
Net Income Applicable to Common Shareholders	$17,233	$7,742	$6,805	($5,237)

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Image Source: http://www.nasdaq.com/

For this project, the market demand is set to 30% of the company's revenue according to the representative's information. For the previous year, this would be equivalent to approx 45 million dollars. The beta for Molecular Devices as released by NASDAQ is 1.11, which is accurate considering their relatively calm stock prices over the last few years. This beta will be used as an estimate for market risk.

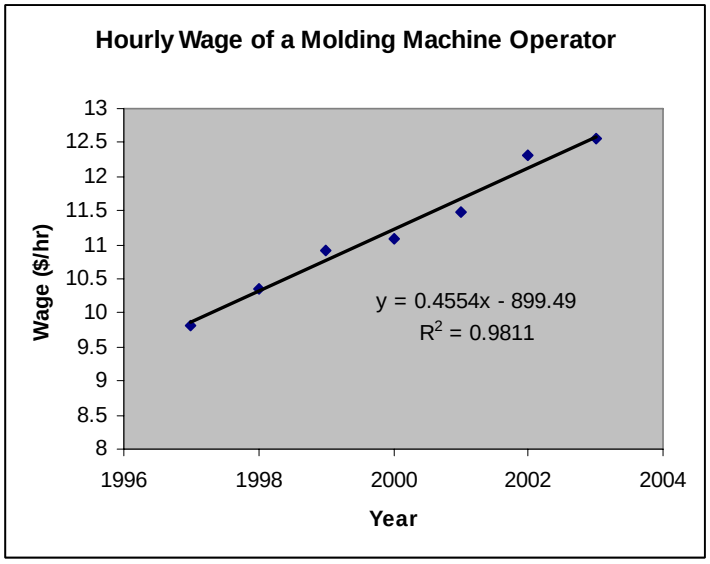
The market demand for Product Line 2 was estimated using company data from Invitrogen, one of the primary suppliers of fluorescent indicator dyes. They had revenue in 2004 if just over 585 million. A source at Draper Lab estimated the percentage of Invitrogens' revenue from fluorescent dies to approximately 40-50%. However, only about 25 % of these dyes sell to a market that would be compatible with Product Line 2. This sets the estimated market for product line 2 at approximately 75 million / year. The total market data for both product lines can be viewed in the following table.

Parameter	Value	STDV	Source
Market 1 Demand	75 (m)	30%	Draper Lab + NASDAQ
Market 2 Demand	45 (m)	10%	NASDAQ
Market Growth 1	22%	10%	Past Company Revenue
Market Growth 2	28%	10%	Past Company Revenue
Beta 1	1.11	20%	NASDAQ-Molecular Devices
Beta 2	0.65	20%	NASDAQ-Invitrogen

As with the previous market, the risk associated with the sensor market can be closely tied with the investment risk of Invitrogen. According to NASDAQ, the Beta for Invitrogen is 0.65, indicating low risk when compared with the market.

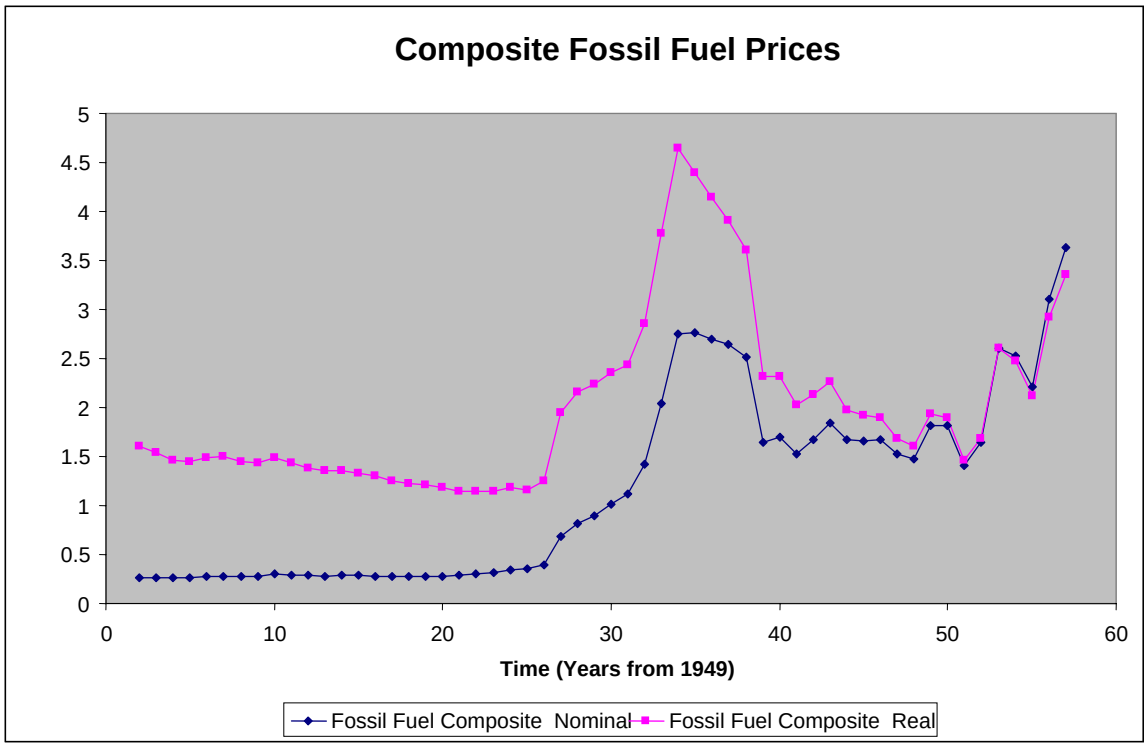
Manufacturing Costs

Labor cost uncertainty was estimated using data from the US Department of Labor (http://www.bls.gov/ncs/home.htm). The following is a plot of labor costs for a typical US machine operator since 1997 as published by the US Dept. of Labor:



The plot dictates an approximate linear trend over the past seven years. This line can be used for future projections and the R^2 value can be used as an estimate of uncertainly in this projection. The above curve can generate a predicted average value at year (t) with a standard deviation.

To predict the cost of energy in the future, previous US data can be analyzed in a similar manner as above. The US Department of Energy publishes the cost of fossil fuel production over the last sixty years.



This plot indicates highly volatile prices over the last thirty years with no distinct trend. The modeling of an appropriate financial model for future energy costs will be a composite of the STDV over the last 15 years (or however many years the forecast is predicting), in combination with a linear fit to the last ten years of data. This will yield a crude, but approximate model for energy costs.

Part 3: Defining System Designs to be analyzed

In the interests of keeping this project simple and to avoid a highly complex model, the list of previously described drug discovery systems have been consolidated into a single marketable product. The system now consists of a single disposable sensor package, which could be used with existing robotic infrastructures. This sensor module would serve as a direct substitute for the fluorescent dyes currently used with 96, 384, and 1534 well plates. As stated previously, the advantage to this sensor module over the traditional dyes is its ability to analyze multiple ions simultaneously without interfering with cellular activity.

To perform a flexibility analysis, the sensor module has been divided into two different design/manufacturing approaches that will affect future cash flows. The systems differ in their size and flexibility of manufacturing. This sensor technology is new and the field of high throughput drug discovery is changing rapidly. For this reason, the calculations will only be performed over a 8 year time period. It would be unreasonable to expect this product will still be marketable or highly competitive after this period of time.

The first system, System#1, consists of a relatively fixed manufacturing strategy that requires a large initial investment. Then sensor module itself would be a single platform containing multiple pre-fabricated sensors for each individual well within the cell plates. This sensor will be referred to as the "Plate Sensor". This design would require a large manufacturing facility due the products size and complexity. To take advantage of economies of scale, a single large plant will be constructed at time zero with a capacity equal to the estimated projected demand at the end of the eight year period. No additional plates can be added or removed over the ten year time period regardless of demand fluctuations.

System#2 is a smaller sensor package consisting of only a single row or column of sensors for each plate. This will be referred to as the "strip sensor" system. This system has the added advantage of letting the user "mix and match" different sensor types in a single plate. From a manufacturing perspective, these strips would require a smaller plant than needed for system 1. This is due to the simplicity and ease of manufacturing of the strips over the large sensor platforms described in system 1. The flexible

advantage to this system is it allows for smaller plants to be constructed over time. As demand increases, additional plants can be built to accommodate unexpected growth. In addition, if demand decreases or manufacturing costs increase, less investment is lost. Since 10-20 of these strips will be required for each plate, economies of scale can be realized for smaller demands than in System 1. This will be highly advantageous if the market demand is lower than the forecasted value.

For each of the two systems described above, a basic set of manufacturing criteria will be developed. These criteria include: minimum plant capacity, plant cost, economies of scale factor, part cost, and demand. These parameters are extremely basic and were gathered as estimates from sources at Draper Lab. They should only be used for this example are not representative of actual facts; however, they do represent the economic properties of each system plan. It must be noted that the demand and economies of scale factors have been normalized between plants. Since 12 sensor strips are required for every single "plate sensor", the economies of scale factor for each plat is adjusted to compensate for this property. The following table shows the economic properties for each production plant.

Property	System # 1	System # 2
Plant Capacity (mill)	24	6
Plant Cost ($ mill)	200	65
Unit Production Cost	50	50
Alpha	0.8	0.6

Table 3.1: Estimated System Plant Data

Part 4: 2-Stage Decision Analysis of Alternative Designs

The following section simulates a two stage decision analysis for each of the two systems discussed above over a ten production period. The uncertainly in this analysis stems from the variability in market demand over time. The following plot displays the revenue of Invitrogen over the last four years. They are the worlds leading sensor dye distributor and would represent the market for these new sensor systems.

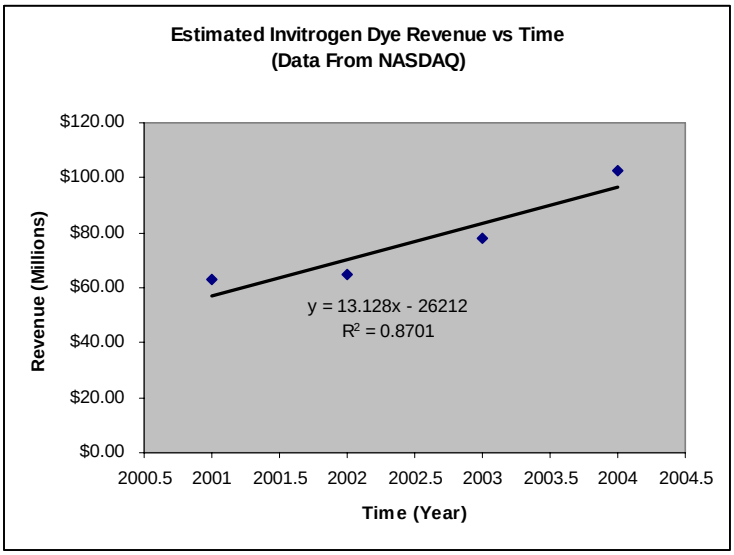


Figure 4.1: Invitrogen Dye Sales

Using this data, future sensor demand will increase at an average rate of 18%, with a variability of ±7% per year. For this analysis, each 4-year period will be designated three possible demand growth rates (11%, 18%, and 25%). After the first five years, the flexible system (System 2) has the option of adding plants based on previous growth rates. The system will assume that the average growth and variability will be the same for the following five years and use expected value information from that point to make the decision. Each demand scenario (low-med-high) has an equal probability (33%).

To calculate each system NPV for all possible market demand scenarios, a basic plant production NPV spreadsheet has been fabricated. The following tables shows how the data is laid out and what factors were used to predict NPV.

Plant Size	1.6							
Alpha	0.6							
Plant Cost	65							
Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Money Demand	100.00	118.00	139.24	164.30	182.38	202.44	224.71	249.42
Unit Demand	2.00	2.36	2.78	3.29	3.65	4.05	4.49	4.99
Plants	2	2	2	2	4	4	4	4
Plant Cost	130				130			
Plant Capacity	3.2	3.2	3.2	3.2	6.4	6.4	6.4	6.4
Production	2.00	2.36	2.78	3.20	3.65	4.05	4.49	4.99
Part Cost	37.89291	41.849	46.219	50.238	54.34	57.854	61.592	65.57
Profits	-67.89	76.15	93.02	114.07	-1.97	144.58	163.11	183.85
PV	-61.7208	76.151	93.021	114.07	-1.966	144.58	163.11	183.9

NPV **711.1002**

Table 4.1: Sample NVP Spreadsheet

The primary advantage to the faxable system is it's ability to choose how many plants to build in year 5. The build / no-build decision was made on the assumption that demand would increase at 18% from its current state after the first four years. After calculations, the optimal strategy was to build 3, 4, or 5 plants depending if the 1st period market demand was 11%, 18% or 25%, respectively. The following decision tree shows all possible outcomes for both plans (Note: Decision node under the flexible plan was omitted to make the tree concise).

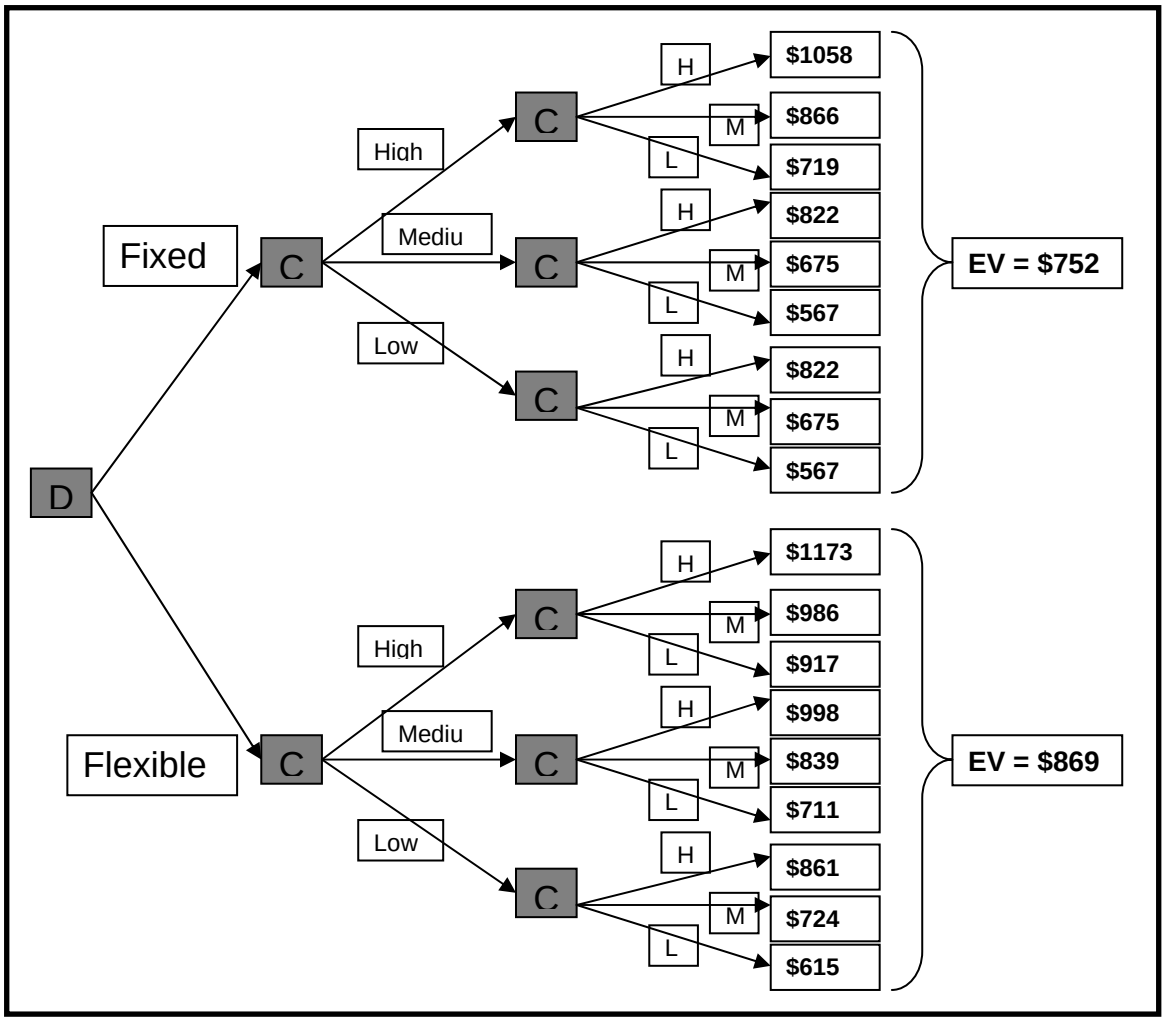


Figure 4.2: Decision Tree

The tree shows a clear advantage in proceeding with a flexible system approach. The flexible system offers over another 100 million in NPV over the eight year period.

Part 5: Lattice Analysis of Evolution of a major uncertainty

The intent of this section is to develop an appropriate lattice depicting the uncertainty of future market demand. The lattice will be projected over the entire eight year period. To develop and accurate lattice model, it is necessary to create an exponential market demand model using existing data. To simulate the market demand for both systems discussed in this report, the cell dye revenue from Invitrogen is used as a model. Using Invitrogen's reported revenue data over the last four years (NASDAQ), the exponential parameters "Ao" and "R" can be formulated. In addition, error bars from the actual-to-fitted data can be used to estimate volatility, or standard deviation. The following plot shows the fitted Invitrogen data along with volatility estimations.

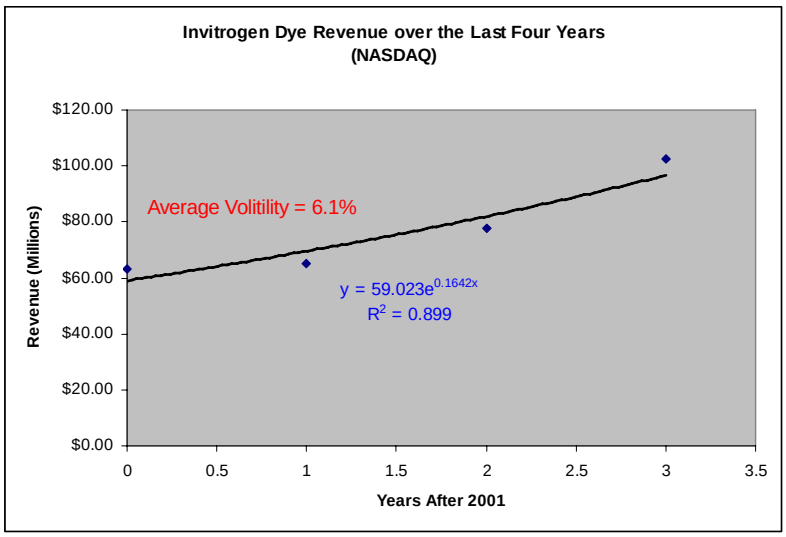


Figure 5.1: Fitted Invitrogen Dye Revenue Data

Since the lattice will be conducted over the eight years following the above data, the "Ao" parameter has been revised to the current revenue value of $102 Million. This will be used as the starting value of the lattice. The following plot shows the estimated revenue trend along with one standard deviations confidence bounds.

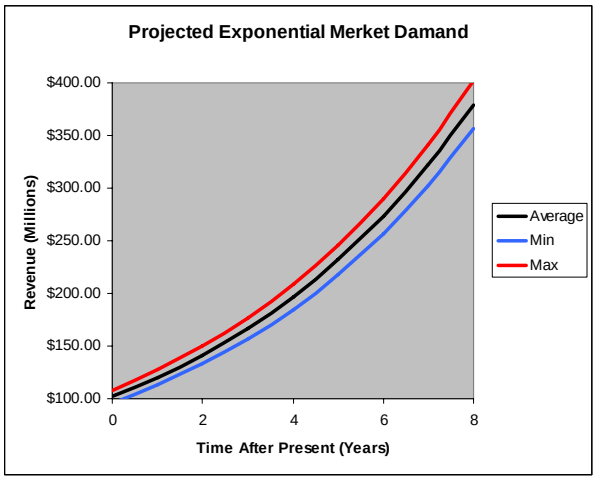


Figure 5.2: Projected Market Revenue

This data can then be used to develop the lattice parameters U, D, P, and Value-Start as defined by the given lattice spreadsheet binomial lattice.xls. Using the fitted data in Figure 1, V=16.42% and σ = 6.1%. The following equations can then be used to calculate the appropriate lattice parameters.

$$u = e \exp(\sigma * \sqrt{t})$$
$$d = e \exp(-\sigma * \sqrt{t})$$
$$p = 0.5 + 0.5 (v/\sigma)\sqrt{t}$$

where:

σ = standard deviation
v = average growth rate (1 time period)
t = time period

Parameter	Values
U	1.0628989
D	0.9408232
P	0.95
P Start	0.95
Value Start	102

Table 5.1: Binomial Lattice Parameters

It must be noted that since the growth rate (V) is larger than the standard deviation, this results in a probability larger than one. To avoid this problem, a probability of 95% was used. The eight year lattice projections from the modified spreadsheet "binomial lattice.xls" can be visualized in the following PDF plots.

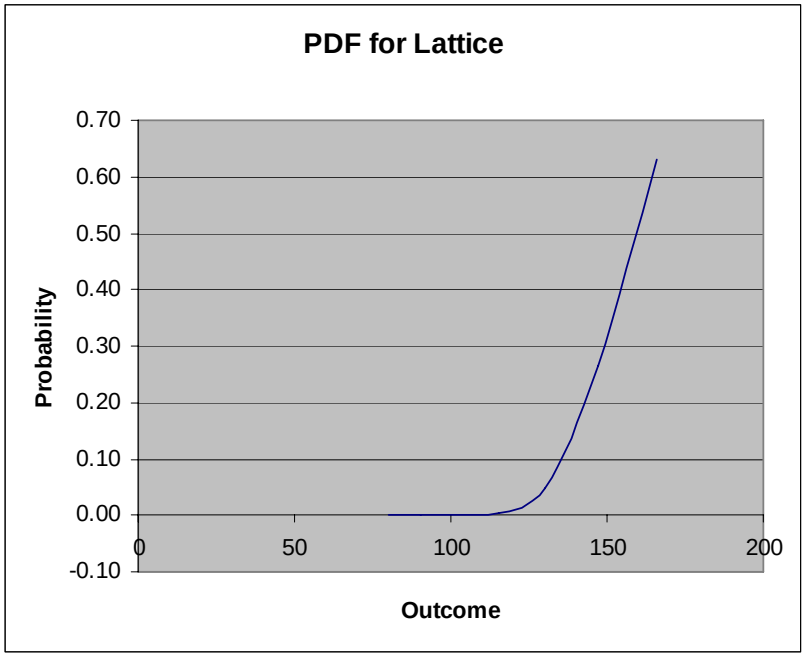


Figure 5.3: Binomial Lattice PDF Plot

Part 6: Decision Analysis Using Lattice

This section of the portfolio integrates an option into the binomial lattice developed in Part 5. The lattice produced in Part 5 predicts the total market demand for the sensor system over an eight year time period. To show the effect of the option on NPV for the system, the cash flow spreadsheet model developed in Part 4 must be integrated with the lattice. This model takes into account run cost, fixed cost, economies of scale, and plant capacity limitations. For each demand state in the lattice, the model calculates an associated profit.

For this exercise, the plant has the option to stop production and sell the plant at any stage throughout the lattice (any year). To ensure the option will be used in certain scenarios, the initial plant capacity is set to the highest project production level. This ensures a loss of revenue if demand is low or production costs are high. The logic behind closing the plant is relatively simple. At each state, if the EV from the next two possible states is negative, the plant closes and the EV from the next period is simply zero. If the EV is positive, the plant remains in operation.

Using the template file "binomial lattice.xls" two resulting lattice spreadsheets was created. It must be noted, that to simplify the simulation, the time period is reduced from eight years to six years. This makes the model simpler and easier to interpret. A six year projection is also more realistic for this type of technology. One sheet in the model contains the EV (NPV) from the lattice with no option. This is calculated as the total NPV for the EV of each year. This NPV will is used as a reference to calculate the value of the option to the project. An example calculation for a yearly expected value is shown below.

$$EV\ (year) = P1*V1 + P2*V2 + P3*V3\ \ldots\ldots$$

$$P = Probability$$

$$V = Value$$

The second sheet contains a lattice that simulated the option to close the plant if demand has dropped too low. The sheet operates with embedded IF statements that decide if the plant should close using the logic described above. The NPV for the project is calculated by working back through each stage (year) of the lattice until the discounted expected values from each stage are brought back to time zero. This NPV can be

compares with the "no option" NPV to determine the value of the option. The logic for the decision can be shown in the general "code" expression below.

IF: (EV next stage) < (Discounted Fixed Cost)

THEN: (EV next stage) = (Discounted Fixed Cost) -> Close Option

ELSE: (EV next stage) = (EV next stage)

The following two sample tables show the outputs from each spreadsheet model, respectively. Also displayed are the input parameters for the particular sample data.

Discount Rate	10%
Plant Capacity (mill)	3.2
Operating Cost (mill)	55
Part Cost ($)	40
Part Retail ($)	50
Alpha	0.6
Initial # Plants	1

Table 6.1: Simulation Input Parameters

Year	0	1	2	3	4	5	6
No Option	-14.3533	-9.7135	-5.2146	-0.8493	3.3891	7.5071	11.5108
		-0.9092	-1.3636	-1.3842	-0.9908	-0.2017	0.9659
			-0.0543	-0.1296	-0.1943	-0.2192	-0.1765
				-0.0031	-0.0103	-0.0205	-0.0308
					-0.0002	-0.0007	-0.0018
						0.0000	-0.0001
							0.0000
EV	-14.3533	-10.6227	-6.6325	-2.3662	2.1935	7.0649	12.2676
PV	-14.3533	-9.6570	-5.4814	-1.7778	1.4982	4.3868	6.9247
NPV (NO)	**-18.4599**						

Table 6.2: No Option Lattice Output

Year	0	1	2	3	4	5	6
Profit Outcome-Option	-14.3533	-1.3758	11.0016	19.9671	24.4890	23.4146	15.6591
	NPV	-18.1844	-14.3533	-10.2248	-4.2216	2.3402	4.1609
			-21.7376	-18.1844	-14.3533	-10.2248	-5.7779
				-25.0310	-21.7376	-18.1844	-14.3533
					-28.0820	-25.0311	-21.7376
						-30.9065	-28.0820
							-33.5196

Table 6.3: Option Lattice Output

For this particular simulation, the fixed run cost was set high and both NPV's for the project are negative. The resulting value of the option is simply (-14.35 –-18.46 =

4.12). To determine the sensitivity of the option to run cost, a single input data table was created to relate option value with operating costs. The figure shown below shows the resulting sensitivity analysis.

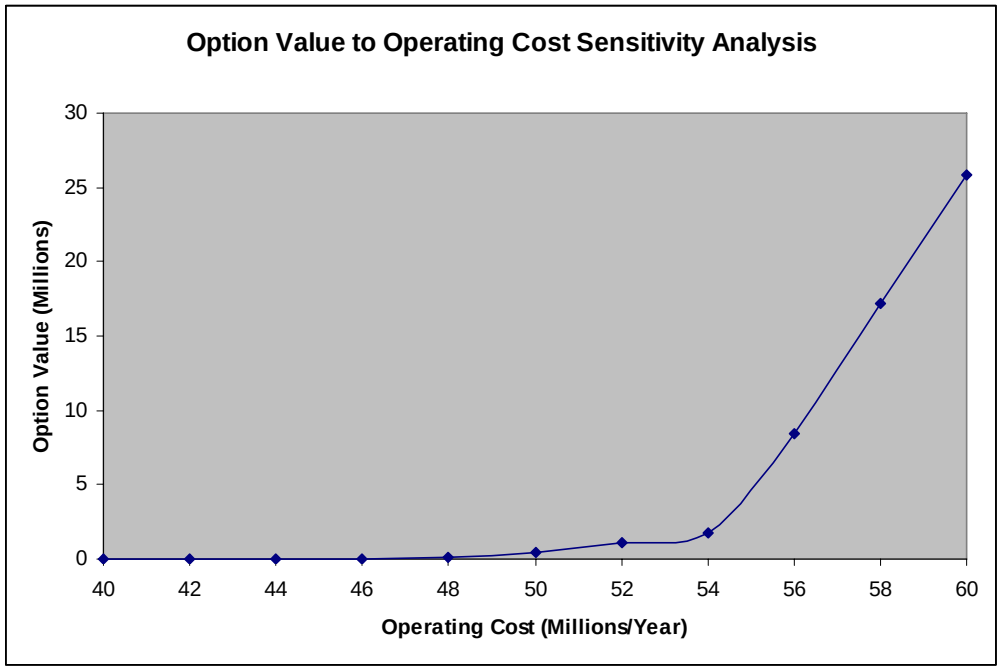


Figure 6.1: Option Value Sensitivity Analysis

The results indicate that the option is only exercised when yearly operating costs exceed approximately 48 million per year. After an operating cost of 54 million per year, the option value begins to increase rapidly in a linear fashion.

The binomial option analysis shows a clear advantage to incorporating flexibility into the system. For this particular example, the option is a "PUT" and is only used when the future outcomes are less desirable than expected. This model also shows how easily system parameters, such as run cost, can affect the value of an option for a system.

Final Conclusions

After completing ESD 71 and this application portfolio, it is apparent that flexible design and valuation of options have obvious advantages in manufacturing applications. This application portfolio was based on a manufacturing system and every concept explored in the course could be used to analyze the system. The concepts used in this course could be used with many other applications; however, manufacturing systems clearly demonstrate the power of such design and analysis techniques.

This application portfolio has been proven very useful in teaching me how to apply valuation concepts to real world applications. However, over the first three parts of the portfolio, it was very unclear as to what variables needed to be modeled in the system. In this case, many areas of the project were researched that had no relevance on the system analysis. I would recommend that future portfolio assignment sheets detail what the system will be used for, or what parameters need to be investigated. Even if students don't understand the analysis techniques, it might help students to choose a system that will show the power of these analysis techniques.

Entering ESD 71, I had a very fixed view on financial modeling. This class taught me how drastically uncertainty can affect the future outcomes of systems. I had always assumed that setting up a system for "average" predicted parameters is an acceptable approach. It is clear that uncertainty can produce a "snowballing" effect that can make future outcomes far different than anticipated. I was very impressed by the power of the binomial decision lattice analysis. Even though it assumes path independence, it greatly reduces the complexity of uncertainly predictions. It is also relatively simple to implement decision strategies within a lattice.