Growth Policies for Biopharmaceutical Companies: A Dynamic Problem Definition

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Abstract

This working paper is an excerpt of the author's Ph.D. dissertation. The excerpt starts with categorizing biopharmaceutical companies according to research technologies applied in drug discovery. Discovery is the earliest phase in pharmaceutical R&D pipelines. The major strategic problem of biopharmaceutical high-technology firms is caused by the length of R&D cycles. What policies (decision rules) ensure sustainable growth if it takes nearly a decade to begin earning royalties from drugs discovered?

System dynamics methodology, on a macro level, is applied to structure and to investigate the problem. First, the usefulness of computer simulation models in understanding growth problems is highlighted. Subsequent sections hypothesize feedback loops causing patterns of growth and potential decline. Analysis on a feedback loop level reveals how mediocre growth decisions can cause corporate decline and ultimate failure. The author's simulation model developed in his Ph.D. dissertation is for testing alternative growth policies. Insights from simulation studies are beneficial for growth management in biopharmaceutical research companies.

Key words: Biotechnology companies, pharmaceutical R&D, strategic decision making, management flight simulator, system dynamics

1. Growth Problems from Duration of Research and Development

Previous explanations regarding research technologies may leave the impression that drug discovery has become a simple task (this is an excerpt of the author's Ph.D. dissertation). This is, however, fallacious. On the one hand, biotechnology and genetic engineering provide powerful tools for identification of novel drugs. On the other hand, however, the entire search process has become increasingly complex. The answer to complexity is research specialization. Biotechnology companies are specialists in novel discovery technologies.

The following table gives an overview of biotechnology company types. The first column repeats those discovery activities already introduced with Figure 4 (see appendix). The second column lists research technologies applied to perform these activities. The third column specifies the category of biotechnology firm.

Table 1: Categorization of biotechnology companies

| Drug discovery activity	Research technology	Biotech company type
Disease target identification and investigation	Gene mapping, Gene sequencing, X-ray crystallography	Genomics companies
Disease target construction for screening[1]	Assays for: gene transcription factors, enzymes, receptors, etc.	Disease target development companies
Compound screening	High-throughput robotic screening	Screening companies
Compound optimization	Combinatorial chemistry*	Combinatorial chemistry companies
Compound production	Recombinant DNA Combinatorial chemistry* Gene therapy (DNA as therapeutic agents)	Biotechnology manufacturer, gene therapy firms

*   Combinatorial chemistry can principally be applied for both the production of compounds and for their optimization (analoging).

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[1]   Two ways of compound screening generally exist: in vivo and in vitro. The traditional in vivo testing means using living animals as disease targets. In contrast, in vitro screening is possible by assays listed in Table 1. The advantage of in vitro screening is that fewer animals are used in pharmaceutical research. The disadvantage is that drug candidates identified may be active in a simple assay-test environment only and that they ultimately fail in more complex organisms.

Some biotechnology companies specialize in only one research technology. Others integrate several and hereby form technology platforms. The expansion of corporate technology platforms is usually directed towards the next step in the activity path, illustrated by Figure 4. This means that a biotechnology firm starts with, e.g. gene identification technologies, subsequently extends into assay development, screening, and analoging. There are many biotechnology firms which are impossible to categorize into either of the stylized company types listed in Table 1.

This study assumes that, after discovery is completed, drug candidates are handed over to collaborators. Collaborative partners are large pharmaceutical firms. They further develop the potential drugs in their own R&D pipeline and, in the case of success, ultimately launch them into worldwide markets. Figure 7 shows R&D pipeline phases and the respective phase lengths.

Figure 7: Time horizons for R&D pipeline phases
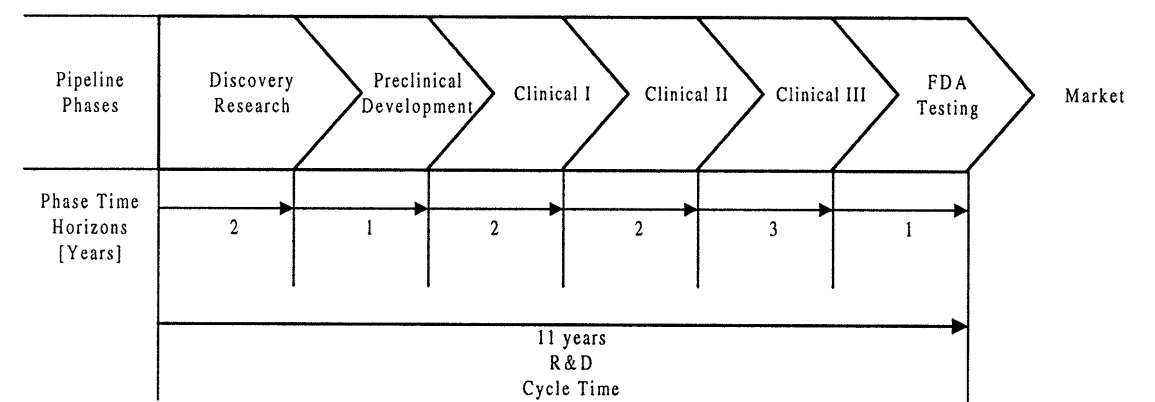
Data derived from: Grabowski, H (1991), Pharmaceutical Research and Development: Returns and Risk, p. 8 – 10, Figure 1. Refer also to DiMasi et al. (1991), Cost of innovation in the pharmaceutical industry, p. 123, Table 3. For reasons of simplicity, integer values measure phase lengths. The values are industry average figures modified to reflect recent trends. For example, the FDA approval phase takes now much less time than in the studies from the early 1990s cited (now 0.5 to 1.0 year). Additionally, the entire development cycle is becoming more efficient with time spans as less as 7 years from preclinical development to market approval.

Figure 7 illustrates that drug candidates require, after their discovery, approximately 9 years in R&D before they generate sales revenues. This long time horizon causes severe cash constraints and forms the central problem for corporate growth of all biotechnology

companies as listed in Table 1. How can such firms achieve sustainable growth if it takes nearly one decade until research results generate revenues from sales?

In contrast, large pharmaceutical firms are able to finance their entire R&D activities with cash from drugs on the market.[2] A biopharmaceutical research company needs to attract alternative sources of investment. Because of the high risks involved in pharmaceutical research these sources are initially limited to venture capital and, later on in the corporate life cycle, to equity investors.[3] Growth of biotechnology companies is severely constraint by the limited access to financial resources.

Achieving a steady flow of sufficient risk capital from venture capitalists or equity investors over many years is of critical importance. Expectations of sufficient returns on investment must be maintained by biopharmaceutical research in order to reward investors for bearing high risks over long time periods. There are three major areas in which management makes decisions to create return expectations:

1. Developing novel research technologies in-house;

2. Integrating forward in the discovery path (Figure 4, see appendix), i.e., expanding the technology platform;

3. Utilizing research technologies for proprietary versus collaborative projects and for research services.[4]

Decisions regarding these three categories are, in principle, the source for growth of all biopharmaceutical drug discovery companies. This is the author's experience gained during his fieldwork. If growth decisions are successful in the eyes of investors, financial

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[2] Debt financing is traditionally very uncommon in the pharmaceutical industry (US Congress (1993), OTA, Appendix C, p. 279.

[3] Even financial institutions (commercial banks) in the United States, which are more risk friendly as their European counterparts, are very reluctant lending money to biotech companies operating in early phases of R&D such as drug discovery.

[4] Collaborative research is funded by large pharmaceutical firms and biotechnology company provide their expertise in novel discovery technologies. Proprietary research is funded by the biotechnology firms themselves, which means that they bear the risk of project failure. In the case of success, however, higher royalties on sales revenues can be negotiated than it is the case for collaborative research. Royalties are a fraction of final net revenues earned by collaborators. If no rights on royalties are obtained, the biotechnology firms' discovery activities are pure research services.

capital will flow steadily to bridge over the time span towards solid revenue streams. The simulation model of this study is a tool to test and design growth policies.[5] Biotechnology companies have to choose policies out of the three growth areas listed previously. A set of decision rules is active at each point in the corporate life cycle. The cycle as simulated begins with the company foundation, it moves through the various life-cycle phases and ends when sales revenues from drugs on the market can sustain growth.

The category of biotechnology company subject to this investigation starts with developing assays (refer to Table 1, shaded area). It expands the technology platform into high-throughput robotic screening and, subsequently, into combinatorial chemistry. A biotechnology firm with these three technologies is considered a fully integrated drug discovery company. This means that it performs the most research activities in-house before preclinical development starts.

The set of growth policies for such a company is not static over the entire corporate life. As insights from the simulation model reveal, the policies have to be composed differently depending on the life-cycle phase a company currently operates. The simulation model addresses the question of which set of policies in what growth stage should be recommended to achieve sustainable growth trajectories.

Sustainability of growth is a critical requirement to maintain corporate independence. A biotechnology company having cash crises usually cannot resolve them without sacrificing corporate control to a larger partner. Recent history shows that under crisis conditions, biotechnology firms are acquired by large pharmaceutical companies or they are forced to merge. Consequently, managerial freedom in decision making regarding the three growth options listed previously is lost. *The ultimate goal of this study is to design growth policies which are robust meaning that corporate independence is maintained*

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[5]   Policies are rules for making decisions.

even under unfavorable conditions. Such circumstances are for instance increasing

competition for research collaborations or drug candidates failing in R&D pipelines.[6]

How important is this growth problem? In the United States, there are approximately

1,300 biotechnology firms with 120,000 employees. Most of the firms can be categorized

into either or several of the firm types listed in Table 1. All European countries lag years

behind the U.S. in terms of the commercialization of novel research technologies in the

field of drug discovery.[7] For many reasons, the transfer of technologies from universities

and research institutes into start-up companies has been much slower in Europe than in

the U.S. The most successful European country is Great Britain with more than 50

biotechnology firms.[8]

The type of research technology applied in these companies is not critical for the problem

under investigation; what is critical is that most of them are exposed to long R&D cycle

as illustrated in Figure 7. The large number of companies suggests that the problem of

this study is important enough to justify serious research effort. Furthermore, the

simulation model presented in this study reveals insights of general importance for

growth control of high-technology companies in other areas such as medical diagnostics,

software development and information technology.

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[6] Corporate independence is ensured as long as biotechnology firms are legal entities as opposed of being an R&D arm of larger pharmaceutical corporations (Roberts, E. B, O. Hauptman (1986), The process of technology transfer to the new biomedical and pharmaceutical firm, p. 110).

[7] Prognos: Kommerzielle Bio- und Gentechnik in Nordrhein Westfalen (1997), Chaper 3: Situation und Entwicklung der kommerziellen Bio- und Gentechnik in den USA – ein Survey.

[8] Arthur Andersen & Co.(1994): UK biotech '94 – the way ahead, p. 29. See also the annual reports of Ernst & Young: Biotech Long-term value short-term hurdles. Considering the high standards in traditional technologies, Germany is one of those European countries being less successful in commercializing novel drug discovery technologies, lacking 7 to 10 years behind the U.S. (Prognos (1997), Chapter 3). The major German biotechnology companies operatin in drug discovery are mentioned in Althaus S. (1997), A fledgling decides to fly, p. V.

2 A System Dynamics Model to Investigate Corporate Growth

The choice of any methodology depends on the characteristics of the problem under investigation.[9] For this study, the problem is the design of policies to achieve sustainable growth. There are three general characteristics of growth policies which makes system dynamics particularly suitable:

1. Management makes growth decisions within positive and negative feedback loops.[10] Such circular causalities do not operate in isolation. Rather, they create networks where loops are interlocking with each other.

2. Corporations are high-order systems,[11]

3. Many relationships relevant for understanding growth problems are nonlinear.

The interplay of these three characteristics constitutes what are called "dynamically complex" systems problems.[12] Such problems are best investigated with system dynamics models. The following discussion, structured by three items, reveals more specifically the usefulness of dynamic models:

1. Characteristics of corporate systems,

2. Learning from computer simulation models,

3. Lack of analytical solutions for corporate growth problems.

Characteristics of corporate systems

Previous research has revealed that the idiosyncrasy of dynamically complex systems can lead to counterintuitive or unanticipated behavior. This may threaten the success of decisions.[13] Current research confirms such observations.[14] Computer simulation is a tool

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[9] Reversing this statement holds true also. The perception of problems depends on the methodology.

[10] In general, any decision continuously made is subject to feedback. This is since accumulations of consequences ultimately feed back to the decision point.

[11] The number of levels, i.e., accumulations such as cash resources or drugs discovered defines the order of a system.

[12] Roberts, E. B. (1964), The Dynamics of Research and Development, p. XX. Sterman, J. D. (1994), Learning in and about complex systems, p. 297-299.

[13] Forrester, J. W. (1969), Urban Dynamics, Chapter 6 (Notes on Complex Systems).

[14] Sterman, J. D., N. P. Repenning, and F. Kofman (1997), Unanticipated Side Effects of Successful Quality Programs: Exploring a Paradox of Organizational Improvement.

for discovering and understanding the characteristics of systems. Insights derived from simulations extend managers' intuition for decision making beyond what is mentally possible. This results in better decisions.

One example on system characteristics is their short versus long term behavior. Although the short-term consequences are often intuitively well understood by managers, the long-term behavior can be counter intuitive and harmful for companies. This is because the internal system structure creates unintended side effects that ultimately counteract what was originally intended by the decision maker.[15] Biopharmaceutical companies have to make decisions to achieve sustainable growth in the short as well as in the long run if they want to stay independent. Knowing that harmful consequences, identified with simulation models, emerge further in the future may alter growth decisions made today.

Learning from computer simulation models

In real life, consequences of management decisions are usually observed after considerable time delays and far from the locus of decision making. Simulation models are tools to compress time and space. This allows to acquire managerial experience in hours which would otherwise be gained in years.[16] Analogous to the purpose of flight simulators used for educating pilots, managers "... can systematically explore the consequences of various strategies (here growth policies) without risking the fortunes of the real enterprise."[17] Computer models provide an interactive learning environment for managers. Insights from simulations yield better decisions than those intuitively made based on simple mental models.

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[15] In system dynamics the term "structure" encompasses a hierarchical order of: the closed system boundary, a set of feedback loops, system states and rates of flow, and the decision rules. Forrester, J. W. (1968), Market Growth as Influenced by Capital Investment, p. 83-86. See also Principle of Systems (1971), Chapter 4.

[16] Bakken, B., J. Gould, D. Kim: Experimentation in Learning Organizations: A Management Flight Simulator Approach, 1994, p. 243-266. See also Forrester, J. W., Industrial Dynamics, Chapter 20: Industrial Dynamics for Management Education, p. 344-361.

[17] Sterman, J. D. (1988), People Express Management Flight Simulator, p. 3. See also: Graham A. et al. (1994), Model-Supported Case Studies For Management Education, p. 219 - 241.

An example of learning about complex systems is discovering and understanding impacts of nonlinearities. Nonlinear relationships may shift loop dominances endogenously.[18] Dominance shifts can carry a system into a mode of behavior, such as from growth to decline or from stability into fluctuations, which may be unexpected and unintended by decision maker. Understanding the consequences of nonlinearities is critical to the successful design of growth policies.

Lack of analytical solutions for corporate growth problems

The high-order and nonlinear characteristics of complex systems listed previously force the investigator to repeatedly search for solutions via computer simulations. High-order systems can be solved analytically only if they are linear. Most systems in the real world, particularly social systems such as corporations, are of a high-order, nonlinear type. Therefore, no closed-form solution can be derived because finding an optimal solution is too complex analytically.[19] Iterative simulations to achieve approximately optimal solutions (in this study the best growth policy for biopharmaceutical companies) is required.[20]

System dynamics is the methodology chosen for this study. It is used to causally understand the dynamically complex growth problem of biotechnology firms.[21] The methodology has been applied successfully to model the growth "problematique" of

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[18] Richardson, G., P. (1995), Loop polarity, loop dominance, and the concept of dominant polarity, p. 67 - 88.

[19] Even low-order, nonlinear systems may be impossible to treat analytically. An analytical treatment is in general only possible with respect to certain aspects of a given low-order system. See for example Blok, M. W. J (1996). Dynamic Models of the Firm. A discussion of analytical solutions versus simulation solutions is in Forrester, J. W. (1971), Principles of Systems, p. 3-5 to 3-11.

[20] Özveren, C. M. and J. D. Sterman (1989), Control theory heuristics for improving the behavior of economic models, p. 130.

[21] An additional strength of system dynamics is that it allows modeling of "soft" variables, which often have a major impact on the performance of social systems. This is not possible in other simulation domains where stochastic systems are investigated. A "quality-of-life" variable, for example, cannot be described with a probability distribution function but it can be modeled in system dynamics (Forrester, J. W. (1971), World Dynamics, p. 60 – 64).

various types of social systems.[22] The holistic and strongly interdisciplinary nature of the problem under investigation requires considerations in very different disciplines like those of drug discovery and corporate finance. In these fields more standard methods such as regression analyses were utilized in addition to system dynamics to address issues related to the problem.

2.1 Model Scope, Boundaries, and Time Horizon

The term "structure" as applied in system dynamics is defined by Jay Forrester and encompasses four components distinguished by the degree of aggregation:[23]

1. Closed system boundary;
2. Feedback loop network;
3. Stock and flow structure;
4. Policies (or, synonymously, decision rules).

This section describes the sources of structure for constructing a model on biopharmaceutical companies. This gives the reader an intuition for what category of information is of critical importance for developing system dynamics models. In the following section, the closed system boundary and the feedback network is presented. Stock and flow structures including policies are discussed in subsequent chapters.

Intensive fieldwork conducted by the author with several U.S. biopharmaceutical research companies is the major source for all four structural components. The firms are mainly located in the State of Massachusetts near the Massachusetts Institute of Technology (M.I.T.). Over 3 years, first as a student and than as a Visiting Scholar and Teaching Assistant at the M.I.T. Sloan School of Management (System Dynamics Group) the author established and maintained working contacts with practitioners in the

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[22]   See for example J. W. Forrester's research on corporate systems: Market Growth as Influenced by Capital Investment, 1968; on urban areas: Urban Dynamics, 1969; on the global system: World Dynamics, 1971.

biotechnology industry. The meetings, usually biweekly, were in the form of company visits, video conferences, and telephone discussions. The research progress was presented and discussed with client companies in various forms: as networks of feedback loops, distributed prior to the meetings, as simulation runs on transparencies, or as stock and flow diagrams with the accompanying equations, generally on the computer screen.

Fieldwork in such depth was required because of the topic's novelty. To the best of the author's knowledge, no attempt at designing growth policies for biopharmaceutical research companies has been made so far in the academic literature. There is not even a body of publications loosely related to that topic. Under such conditions, modelers are generally forced to actively seek experience from those practitioners who are confronted with the problem. Book knowledge may be considered a sufficient substitute for practical experience only if the problem under study is well grounded in the literature.

Even under such conditions, contact with the "real world" is critical since the ultimate goal of any system dynamics model is the design of decision rules to improve system performance. In order to achieve this objective, "… system dynamics models rely heavily on information that is known only to people who are working within the system: book learning and statistical information are seen as useful but entirely inadequate: one must accept the knowledge of practitioners."[24] In essence, the question is, from where, if not directly from the decision-maker, should the modeler obtain key information regarding the way in which decisions are made? It is the decision process which is frequently described poorly and, for the purpose of constructing useful system dynamics models, insufficiently in academic literature.

As a result of the fieldwork, Figure 1 illustrates, in the highest aggregation level possible, the model scope and boundary. This diagram is intended to give an overview on the subsystems and the major concepts modeled within. Only main links and concepts are

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[23] Forrester, J. W. (1968), Market Growth as Influenced by Capital Investment, p. 83-86. See also Forrester, J. W. (1971), Principles of Systems, Chapter 4.

[24] Forrester, J. W., System Dynamics as a Vehicle for Teaching Economics, Departmental memorandum (D-4725-1), p. 4, System Dynamics Group, M.I.T. Sloan School of Management.

shown in order to keep it simple. For example, a direct link is missing between the sector "Discovery Research" and the sector "Collaborative/Proprietary Projects" on the top left side of the diagram. The connection would indicate that a biotechnology firm can accept collaborative research only to the extent that capacity is available. In case the company's biotechnological research is very attractive to large pharmaceutical firms the biotechnology company will turn down collaborative offers if there is no free capacity. Another example of omitted concepts is the diversity of "Compound Library." The compound library is placed in the middle of the diagram and its diversity determines research results (lower left). This is not illustrated by a link to insure the overview's simplicity.[25]

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[25] The concept of compound diversity is discussed in the Ph.D. dissertation.

Figure 1: Model scope and boundary diagram
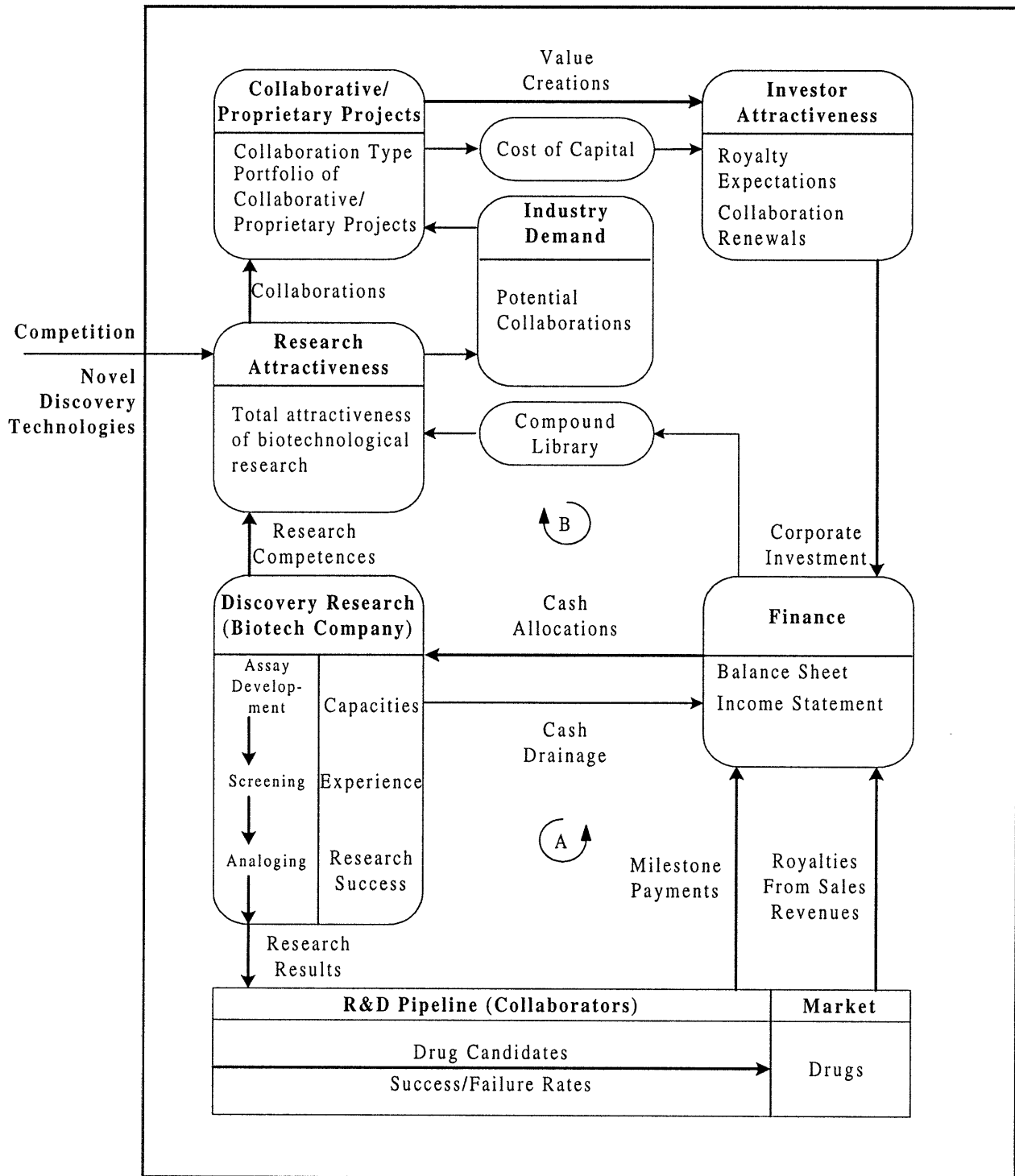
The diagram indicates that, because of sector-interconnections, decisions made within one subsystem may cause problems or create opportunities in other areas. Understanding the sector specific consequences of decision-making is a key objective of the simulation model. The model boundary is illustrated with a frame around the subsystems. The exogeneous inputs are outside this boundary.

The boundary diagram shows one facet of the feedback problem here under investigation with loop signs placed in the middle of the picture. On the bottom-half of the diagram, the A loop (counterclockwise) operates in the long run when cash is flowing into the biotechnology firm first from milestone payments and then from sales revenues (bold arrows). In the short and medium run, the corporate survival depends on the B loop (clockwise) in the top half of the diagram.

The starting point of the B loop is at the middle-left of the picture, where competence in biotechnological research determines research attractiveness and consequently access to collaborators (bold arrow). Resulting drug candidates create economic values and thus attractiveness to investors. Their financial resources will be invested in discovery technologies which increases research competence. The B loop is operating in the long run also, but at a decreasing importance as the A loop becomes stronger.[26]

To fully capture the dynamics of such growth loops, the model uses a 25-year time horizon. In general, the horizon-length depends on the time frame over which the dynamics of the problem unfold. R&D cycles usually take more than one decade until drugs are launched. Furthermore, the first part of the market cycle, which is patent protected, adds another 10 years.[27] The five years remaining to a 25 year time horizon should capture a ramp-up phase due to corporate formation and likely delays in the R&D cycle. The total horizon in this model, therefore, spans the life cycle portion for

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[26] Both loops are reinforcing. The next section presents in addition the negative loops hypothesized.
[27] The assumption for this study is that biotechnology firms receives no royalties after the patent protection ends.

biotechnology companies starting at their formation until sales revenues from the first drugs end.[28]

As illustrated in the boundary diagram, structure relevant to capture the problem is to a large extent endogenously modeled: drug discovery activities, flow of drug candidates through R&D pipelines, corporate investments and financial resource allocations for research capacities, etc. are determined within the model boundary. The strength of competition for research collaborations is an exogeneous variable. Another external input is emerging discovery technologies, which could substitute for the technologies currently applied in the biotechnology firm. This input is used to test the behavior of the biotechnology systems to external shocks from new technologies.

Table 1 summarizes the key variables which are modeled endogeneously, exogeneously, or which are excluded from consideration. The choice between these three categories depends on (a) whether a variable is important for portraying the problem and (b) to what extent it is important. Those variables required to explain major problem characteristics are modeled endogeneously. Outside the model boundary are variables which have impacts on problem behavior but no significant reverse causality exists. Such variables are not part of critical feedback loops. Excluded are those variables which are either summarized in aggregated metrics or which are irrelevant for understanding the problem.

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[28] Time horizons for system dynamics models are generally selected according to the period over which the dynamics of key variables unfold. This assumes that major feedback loops operate in the same time domain which is usually the case but not in this study. Here, the time over which major feedback loops operate sums up to more than two decades. In contrast, the dynamics of variables, like those for research capacity expansion, plays out after a few years required to build up laboratory equipment and to train scientific personnel.

Table 1: Model boundary

Endogeneous	Exogeneous	Excluded
Drug candidate success and failure Drugs on markets Financial statements Investment decisions Resource allocation to discovery technologies Experience accumulation Research capacities (scientists and laboratory equipment) Cost reduction through learning Attractiveness of technology platforms Research portfolios: collaborative versus proprietary projects Compound libraries Cost of capital (rate of return expectations)	Research capacities (and experience) of competing biotechnology firms and collaborators Change to novel discovery technologies Competition on drug markets	Disease target identification (gene discovery) Selection of disease targets for drug discovery Scientific details like: evaluation of toxicity, efficacy, bioavailability of drug candidates, etc.

2.2 Dynamic Hypotheses on Growth Trajectories

System dynamics rests on the assumption that structure determines behavior.[29] System structure consists of the four components listed previously. System behavior or, synonymously, its "dynamics" refers to change over time. All system dynamics models are theories of how structure causes problematic behavior.

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[29] Graham, A. K. (1977), Principles on the Relationship Between Structure and Behavior of Dynamic Systems.

This section presents reference modes, that is the behavior of key variables associated with growth of biotechnology firms. The author developed the modes based on discussions with managers in the biotechnology industry. The reference modes are therefore data used later on for assessing the model's validity. Deriving reference modes is the second step in the model construction process after the problem is defined. In addition, this section organizes variables and their interrelations in causal loop diagrams. By comparing reference modes with causal loops, hypotheses are examined on how feedback structures may cause problem behavior.

Feedback loops represent dynamic hypotheses and mathematical simulation models are required to test them. This is because the polarity of causal loops is in most cases insufficient for reliably anticipating the dynamics they cause.[30] For instance, a positive feedback loop does create exponential growth only under the condition that a disturbance of one loop variable in an upward direction is, after propagating around the loop, amplified.[31] It is the strength of a reinforcing loop, which determines whether the resulting behavior is exponentially growing or decaying.[32] Quantification of causal relationships in stock and flow structures and their simulation is the only way to determine system behavior with confidence.[33] The fact that feedback loops are ambiguous limits the ability for deriving modes of system behavior from loop polarities. Only simulation runs of a mathematical model can verify or falsify feedback loops initially hypothesized.

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[30] Another reason for the term "hypothesis" is that during the process of model building and simulation it may turn out that the original feedback loops are incorrect since the problem was ill-perceived. As learning from the model proceeds the dynamic hypothesis are modified or replaced by more appropriate feedback structures.

[31] In control theory, the loop strength is measured by the "gain." A positive loop is only exponentially growing if the loop gain is larger than one (Richardson, G. P. and A. Pugh, System Dynamics Modeling with DYNAMO, p. 167, fn. 7).

[32] Exponential decay is caused by a loop gain smaller than one.

[33] A critical aspect of complex systems is that the strength of causal loops changes over the time of simulation. For example, nonlinear formulations can cause shifts in loop dominance converting an exponentially growing loop into exponentially decaying behavior or vise versa. It is usually impossible to anticipate dynamic consequences of nonlinearities by mental simulation. An excellent discussion on the limits of causal loop diagramming is in Richardson, G. P., Problems with Causal-Loop Diagrams, Departmental Memorandum (D-memo 3312).

The purpose of presenting causal diagrams is to communicate to the reader the essence of model structure assumed in this study. Causal loops are a very useful tool for illustrating dynamic problems in a simple and concise manner. No scale for the reference modes appear on the y-axes. This is because qualitative properties of behavior are much more important at this point than precise numbers. No years are specified on the x-axis for the same reason. The section presents seven dynamic hypotheses. Three of them are growth hypotheses equivalent to the three categories of growth policies discussed previously.[34] One is a hypothesis on growth saturation and the remaining three are on corporate decline. In summary:

1. Hypothesis: Corporate growth is generated through developing novel research technologies.
2. Hypothesis: Limits to growth due to optimal research capacities.
3. Hypothesis: Expansion of technology platforms creates corporate growth.
4. Hypothesis: Proprietary research creates corporate growth.
5. Hypothesis: Lack of continuous research success causes corporate decline and unfavorable environmental conditions enforces this trend.
6. Hypothesis: Technology platforms being to broad cause corporate decline.
7. Hypothesis: Future cost burdens cause corporate decline.

1. Hypothesis: Corporate growth is generated through developing novel research technologies and
2. Hypothesis: Limits to growth due to optimal research capacities.

The expression "novel" refers here to new types of assays. Assays are disease targets required in compound screening. The term "research technology" is synonym to research capacity which is used from now on since it is a more tangible expression. Capacity consists mainly of scientists and, to a minor extent, laboratory equipment. Corporate growth comes only form successfully applied research capacity. Therefore, Figure 1 illustrates the reference mode for the portion of assay capacity which produces research results and not failures.

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[34] See author's dissertation.

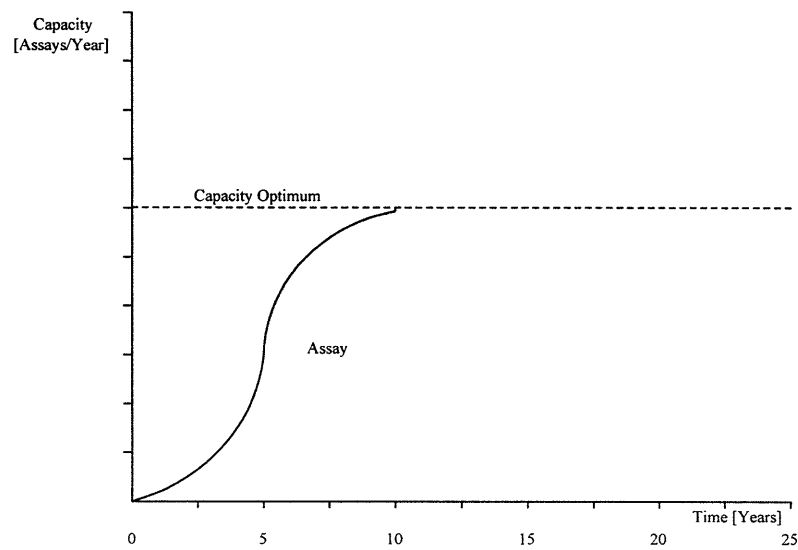*Figure 1: Reference mode on successful assay capacity*

Figure 1 assumes a logistic shape for assay capacity. The low initial growth rate is due to factors related to the technology novelty. Time is required for tasks like hiring appropriate scientists, their training, accumulating research experience, and building adequate laboratory equipment etc. Such factors initially suppress research successes.

The expansion of assay capacity becomes easier with experience and as organizational routines are established. This reflects a rapidly increasing capacity growth rate. As the capacity approaches a desired or optimal value there is less need for its expansion and growth rates start to decline. The capacity optimum, illustrated with a dashed line in Figure 1, reflects limits in duplicating research activities within the organization of a biotechnology company.[35] Note that assay capacity on line reaches its optimum well before the 25-year time horizon ends.

Figure 2 portrays the causal loop structure hypothesized for generating the reference mode on assay capacity.

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[35]   For a discussion on optimal research capacities see the dissertation.

Figure 2: Dynamic hypothesis on capacity expansions
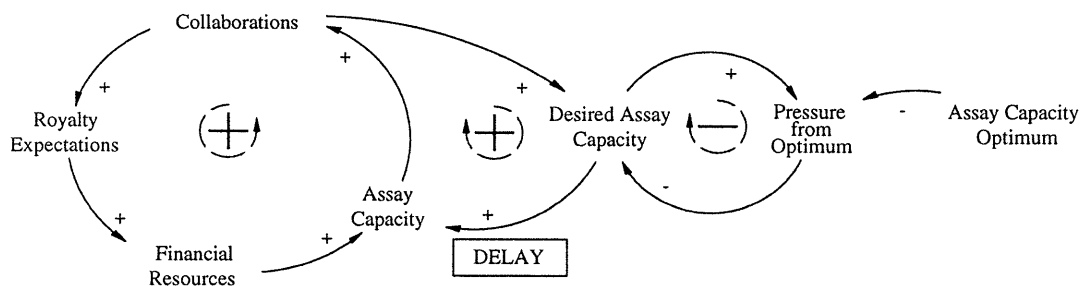
Arrows indicate causality. A variable X on the arrow tail is causing a change of the variable Y on the arrow head. The plus sign indicates that X and Y tend to move in the same direction and a minus polarity means that X and Y tend to move in the opposite direction. Specifically, a plus polarity means that, all else being equal, if X increases (decreases), then Y increases (decreases). The partial derivative $\partial Y/\partial X > 0$. A minus polarity means that, ceteris paribus, if X increases (decreases), then Y decreases (increases). The partial derivative $\partial Y/\partial X < 0$.[36]

The first loop on the left is reinforcing. This loop is presumably most important for driving corporate growth before market launch of drugs. As long as drugs are in R&D pipelines investigated, biotechnology firms receive financial resources because of investors' *royalty expectations* (left variable). Royalties are a fraction of those sales revenue collaborators receive for marketing drugs originally discovered by biopharmaceutical companies.

As *royalty expectations* increase, the firm's attractiveness to investors rises resulting in additional *financial resources* which are used for *assay capacity* expansions. More available research capacity allows the company to agree on additional *collaborations* and the resulting drug candidates lead to further increasing *royalty expectations*.[37] This closes the positive loop.[38]

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[36] Partial derivatives for interpreting polarities of arrows are always correct. The verbal definitions traditionally applied are usually correct. In some cases, however, when an arrow illustrates a rate-to-level link, they are false. Such cases occur at least once in every loop. An example is in Figure 2 between "Pressure from Optimum" and "Desired Assay Capacity." The pressure variable limits the growth rate for desired capacity modeled as a level. An increasing pressure does not decrease the capacity goal as the verbal definition of the (-) sign suggests. This definition has in such cases to be modified to: an increase in pressure results in a value for desired assay capacity which is *less* than it would have been without a change in pressure. See Richardson, G. P. (1981), Problems with Causal-Loop Diagrams, p. 6. Arrows in causal loops do not indicate correlation in a statistical sense. See Richardson G. P. and Pugh, A. L., System Dynamics Modeling with DYNAMO, p. 238 - 240.

[37] The model assumes that after finishing collaborative research only *the* most promising drug candidate is developed further in collaborators' R&D pipelines. Pharmaceutical companies cannot finance the

By embarking on more collaborations the *desired assay capacity* increases which, after a time delay as depicted in Figure 2, results in more assay capacity on line and subsequently additional collaborations.[39] This closes a second reinforcing loop. Both positive loops are presumably causing the exponentially growing section in the assay capacity graph illustrated in Figure 1. These positive loops do not grow without limit, however. As the capacity goal approaches the *capacity optimum*, pressure increasingly suppresses goal expansions. The negative feedback loop on the right of Figure 2 is getting stronger and ultimately controls growth of the second and, after a time delay, the first reinforcing loop. The exponentially growing capacity therefore converts into a goal-seeking mode (Figure 1).

The *desired assay capacity* is a fixed value when it reaches its optimum. This suggests that *assay capacity* on line finally levels off at the optimum as illustrated in the reference mode of Figure 1. The reinforcing loops stop growing. *Assay capacity* on line is then constant, the number of collaborations and, ultimately, the royalty expectations level off also. These variables reveal a reference mode of a logistic type similar to assay capacity. The variable *financial resources*, however, does not follow such a mode as discussed next.

The first dynamic hypothesis reveals very different behavior in the financial domain. Figure 3 illustrates reference modes of major financial variables.

development of all compounds discovered. Consequently, as the number of collaborations levels off so does ultimately the number of drug candidates in R&D and therefore royalty expectations.

[38] Biotechnology firms developing only assays hand them over to larger partners who screen their compound library against these disease targets. The drug candidates discovered through screening create royalty expectations.

[39] Loops illustrate only major time delays. There are delays in all other linkages also such as the perception of royalty expectations by investors.

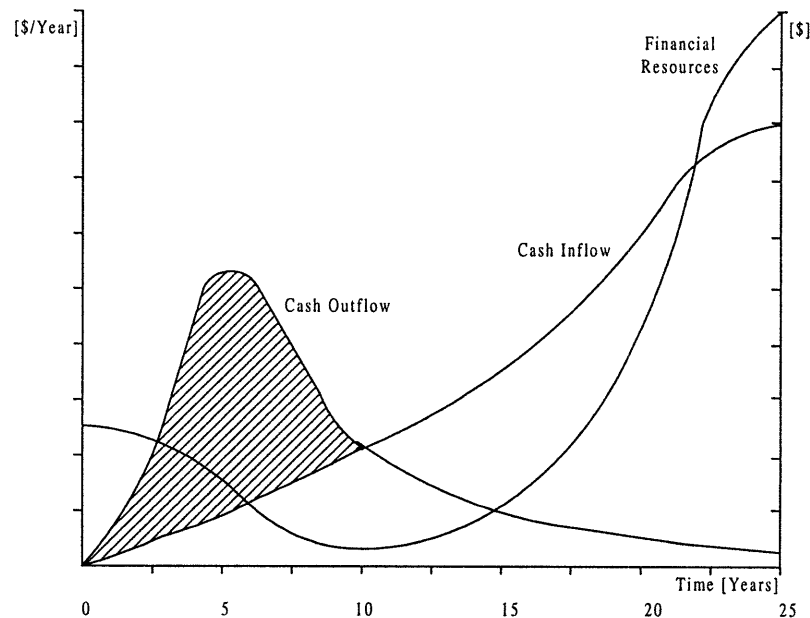*Figure 3: Reference modes on financial variables*

Figure 3 shows the dynamics of: cash outflow, cash inflow, and financial resources. The cash outflow and cash inflow graphs represent rates of change and the units are dollar per year qualitatively measured by the y-axis on the left side. Financial resources is the integration of both rates and its units are dollars measured by the right y-axis.

The cash outflow graph is an aggregate for all expenditures a biotechnology company incurs. Expenses for developing assay capacities are predominantly driving the cash outflow curve in the initial years of corporate life. The first section of this curve, until its peak, are mainly investments for expanding assay capacity. Around year five, capacity expands at a decreasing rate and therefore the investment curve reaches its maximum at that point and declines subsequently. At year ten, capacity reaches its optimum but the cash outflow graph does not fall to its lowest level where reinvestment is the main expense to compensate for depreciation. The research organization is still in an early stage of corporate life where experimentation is required and administration is built up. At the end of the time horizon, the investment level reaches its minimum necessary to sustain an optimum of research activity.

Over the entire 25-year time period, biotechnology companies receive cash flows in various forms such as:

1. Payments for collaborative research;

2. Investments due to royalty expectations;

3. Milestones for successfully developing drug candidates;

4. Royalties.[40]

The cash inflow curve in Figure 3 is an aggregation of these four items. Large partners fund collaborative research such as expenses for scientists and material needed but not those incurred for expanding research capacities. In addition, collaborators contribute to only a fraction of overhead. In Figure 3, the total cash inflow rate is significantly lower than the cash outflow rate and therefore the pool of financial resources decreases, starting from an initial endowment at year zero. The difference between cash inflows and cash outflows is the shaded area in Figure 3. At year ten, inflows and outflows are equal and consequently the graph for financial resources reaches its minimum.

After the first decade, the cash flow curve continues to rise exponentially for several reasons:

1. Biotechnology companies become increasingly attractive to investors since drug candidates move forward in the R&D pipeline and therefore closer to the marketplace;

2. Milestone payments arrive for drug candidates proceeding successfully through late development phases;

3. Royalty payments are made on drugs launched.

Because the cash inflow graph stays above the cash outflow curve, financial resources increase continuously. The graph rises at a higher rate than the cash inflow curve because investments and therefore cash outflows continue declining. Towards the end of the 25-year time horizon, cash inflows level off. This is because assay development capacity

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[40] Research grants from governments can be another source of cash flow. Government research is excluded from consideration.

stays constant at its optimum reached at year ten (Figure 1). A fixed assay capacity limits the number of disease targets to be developed and therefore constrains the number of drug candidates or projects to be processed in R&D pipelines.[41] As the number of projects in R&D pipelines eventually levels off, milestone payments and royalties will reveal the same mode of behavior. Consequently, the cash inflow graph grows at a decreasing rate towards the end of the time horizon in Figure 3. The pool of financial resources levels off also. Again, these reference modes are qualitative estimations of expected model behavior. Figure 4 depicts feedback loops hypothesized with financial variables just discussed. They presumably generate reference modes portrayed in Figure 3.

Figure 4: Dynamic hypotheses on financial variables
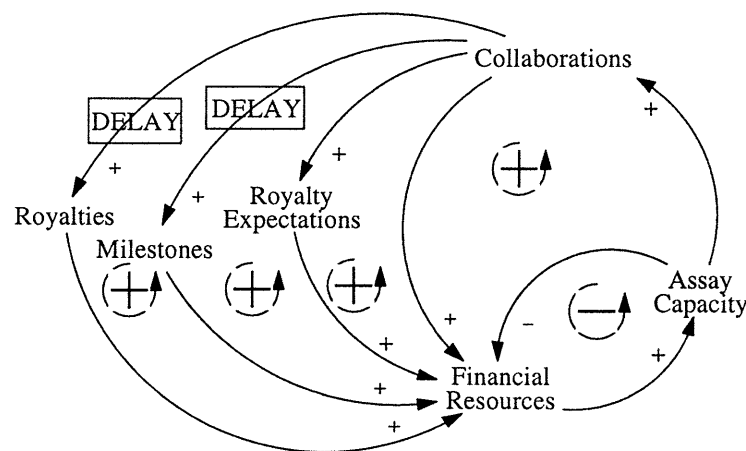
There are four reinforcing loops arranged according to the strength of their time delays. As the reader moves from the right to the left side of the diagram, the delays increase. In other words, feedback loops operate more slowly. The specific links refer to:

1. Collaborators pay research expenses as they occur (inner link from *collaborations* to *financial resources*).

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[41] The assumption is that only the most promising drug candidate per disease target is developed further in R&D pipelines.

2. There is a small perception delay for royalty expectations on the investors' side. This delay is not indicated by a rectangular delay symbol since it is short relative to the years it takes for

3. receiving milestone payments and, ultimately,

4. royalties.

The cash flow link in the reinforcing circle on the very right operates quickly but is much weaker than the balancing loop. This drains financial resources in Figure 3 until loops on the outside become sufficiently stronger.[42] The implicit goal of the balancing loop is zero financial resources. At zero capital, biotechnology firms are constrained to investing cash as they receive it. This condition is not sustainable in a start-up company with continuously high needs for investment capital.

Figure 5 depicts a slightly different view on corporate growth measured by a variable labeled "Cumulative Cash Flow (CF)."

---

[42] The reference mode for financial resources in Figure 3 represents an aggregated behavior over a 25-year time horizon. Over shorter time horizon, this pool of cash may increase or decrease strongly after rounds of raising equity on capital markets are completed or after acquiring research capacities. Figure 3 portrays the general trends.

Figure 5: Reference mode on cumulative cash flow (CF)

[$]

positiv

Break-Even Point

Time [Years]

0   5   10   15   20   25

negativ
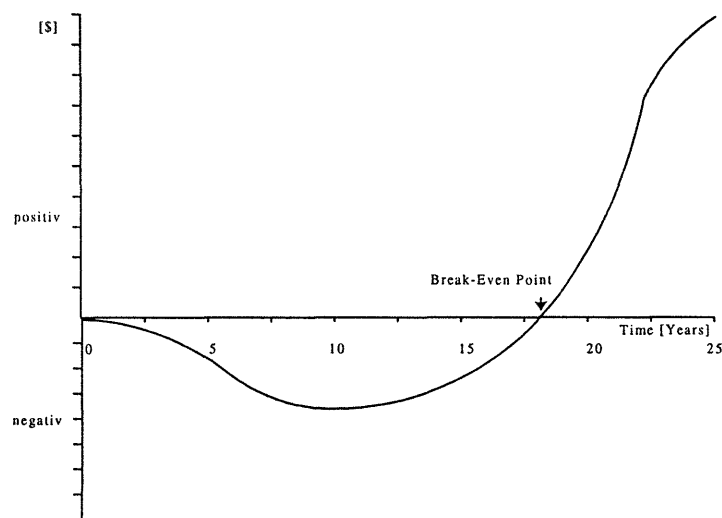
The accumulation of the difference between cash inflows and outflows of projects is frequently graphed with a behavior mode similar to the CF graph of Figure 5.[43] The purpose is to illustrate initial investment periods where cash outflows are larger than inflows from project results. Therefore, the CF becomes increasingly negative. Break-even points are achieved when the cumulative inflows outweigh previous investments. This concept is now applied to biopharmaceutical companies as a whole.

An equivalent application would mean that cash inflows reflect what was *directly* earned from research operations and by research results. All items listed on page 42 fulfill such a requirement except the "investments due to royalty expectations." This item has to be excluded since it is not directly earned through research activities or results. Consequently, the cash inflow graph required for deriving the CF lies below the inflow curve illustrated in Figure 3. The cash outflow is identical to the one in Figure 3.

Since the subsequent analysis is qualitative it is legitimate to neglect the differences in cash inflows caused by "investments due to royalty expectations." This makes it easier to convey the following ideas by directly referring to Figure 3. The CF curve is then derived

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[43] Freeman, C., Soete L. (1987), The Economics of Industrial Innovations, p. 246. See also the working paper of Shah, S. and E. Garnsey (1993), The Acquisition of High Technology Firms: Evidence from Cambridge, p. 14-20.

by shifting the financial resources graph in Figure 3 downwards by the intercept so that the CF curve starts at the origin.

The CF is the integration of the difference between both rates illustrated in Figure 3. Integrations are the areas under rate curves. By examining these areas in Figure 3 it is obvious, that the CF graph decreases in the negative domain during the first decade. The CF curve reaches its lowest point when no shaded area is left. As soon as the areas under both rate curves are equal, the CF graph crosses the x-axis and becomes positive. This break-even point is around year 18 and it is reached long after cash inflow is above outflow.[44] In other words, net earnings would be positive after the first decade as soon as both rates intersect.[45] However, it takes much longer for biotechnology firms until the cumulative returns earned from operations outweigh total investments.

3. Hypothesis: Expansion of technology platforms creates corporate growth

The term "expanding" means that novel research technologies are added to those already existing within a biotechnology company. This broadens its technology or, synonymously, the capacity platform. The expression "novel" refers here to the drug discovery activities of robotic screening and to analoging by combinatorial chemistry. Figure 6 shows the reference modes for both technologies in addition to assay development.

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[44] This is a specific observation of the general fact that accumulations lag inflows. For instance, given a sine wave inflow and a constant outflow with the same intersect (y-axis value at time zero). Their accumulation reveals a 90 phase lag to the inflow rate.

[45] Net earnings would be the difference of both annual rates: operative cash inflow and investment. No interpretation of such financial terms in an accounting sense is appropriate due to the high level of aggregation required at this point.

*Figure 6: Reference modes after technology platform expansions*
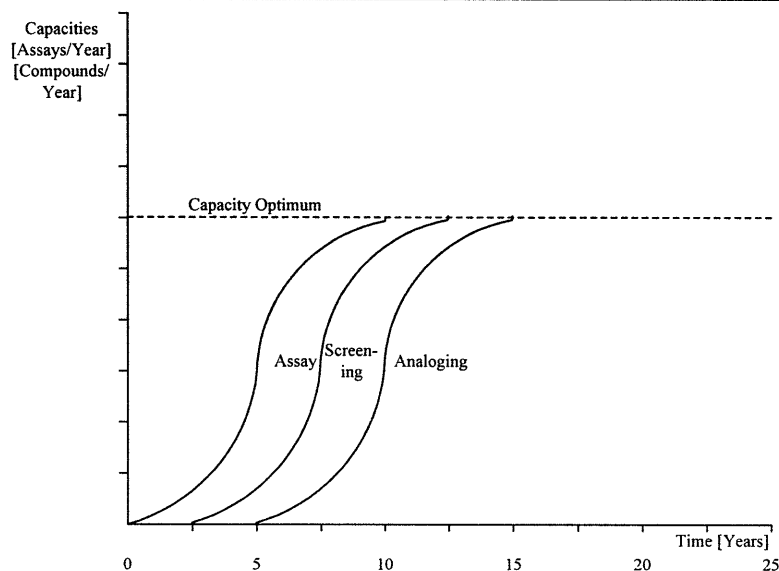
The y-axis qualitatively measures screening and analoging capacities in compounds per year in addition to the units for assay capacity. The behavior patterns are logistic for reasons analogous to those discussed in the assay capacity case. Figure 6 also indicates that there is a capacity optimum for screening and analoging depending on assay capacity.[46] No additional capacity is useful downstream if insufficient assays are developed.[47]

The reference modes of financial variables, presented in Figure 3, do not change qualitatively. For this reason they are not replicated. The modes of behavior change quantitatively, however. The cash outflow rate will have a higher peak and declines more gradually in order to finance the technology platform expansion. The area under this curve will be much larger. It is expected that cash inflows are higher also which shifts the curve above the one illustrated in Figure 3. Reasons for that are discussed within the context of the following dynamic hypothesis.

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[46] For reasons of simplicity, screening and analoging capacity optima are illustrated as equal which is not assumed for the simulation model.

[47] Refer to the drug discovery path in the appendix for interpreting the term "downstream."

Figure 7: Dynamic hypothesis on technology platform expansions
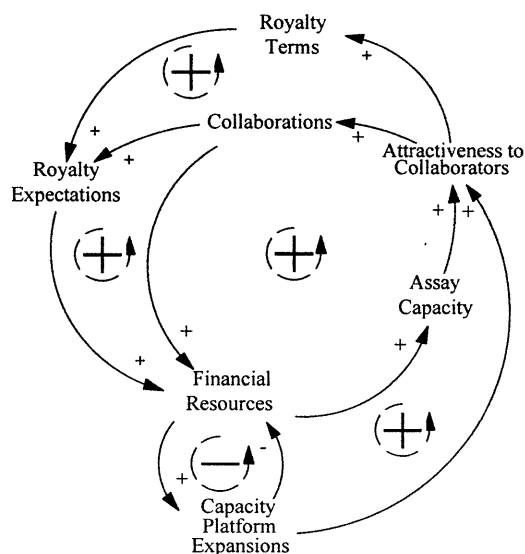
The inner growth loop has an additional variable labeled *attractiveness to collaborators* for facilitating explanations. To keep Figure 7 easy to understand, it illustrates only those loops around the main growth loop which are *added* by the third hypothesis.

Capacity platform expansions drain financial resources as depicted by the lower negative loop. However, biotechnology firms can perform more research activities of the drug discovery path which increases their *attractiveness to collaborators*.[48] This results in (a) more collaborations and (b) better *royalty terms*.[49]

Since the biotechnology firm performs more activities in the drug discovery path, it has a stronger negotiating position with large pharmaceutical firms. This results in higher *royalty terms* and *royalty expectations*. The milestone and royalty loops on the outside of Figure 4 are stronger. Consequently, the cash inflow increases at a higher rate than it is the case with assay development as the only research technology. These effects are summarized by a CF shown in Figure 13 at the end of this section. The curve labeled

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[48] Refer to the appendix for an illustration of the drug discovery path.
[49] Since research projects run over a broader technology platform, the collaboration type changes also. Biotechnology firms negotiate assay *and* screening collaborations after expanding the technology platform into robotic screening.

"Capacity Platform Expansions" has a greater minimum than the original one named "Reference Trajectory." The reference case is for assay development only. The upward trend is stronger, potentially reaching the break-even point earlier. The next hypothesis is regarding proprietary research projects.

4. Hypothesis: Proprietary research creates corporate growth

The assumption of the previously presented hypotheses is that research capacities are applied for collaborative research only. Under such conditions research expenses are paid by collaborators. Another option would be proprietary research in which biotechnology firms pay all the expenses. This means that they bear the risk of failure but, as a reward on taking that risk, the firms can demand higher royalty fractions from sales revenues in the case of research success. The drug candidates discovered are then handed over, at some stage in the drug discovery path, to collaborators for further clinical development. The next figure shows the fourth dynamic hypotheses.

Figure 8: Dynamic hypotheses on proprietary research
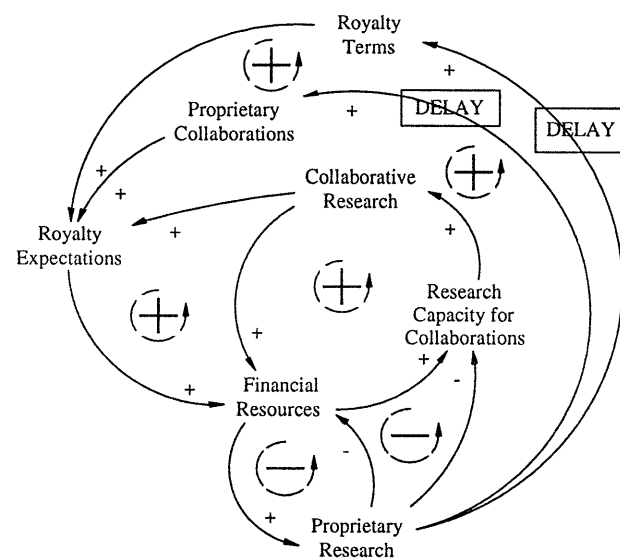
The policy on proprietary research has different impacts depending on the time frame: in the short run it drains *financial resources* and reduces available *research capacity for*

collaborations. This further limits the cash inflow from collaborators (balancing loop on the bottom right of the diagram). However, after a research delay, royalty expectations increase if collaborators are found for proprietary drug candidates.
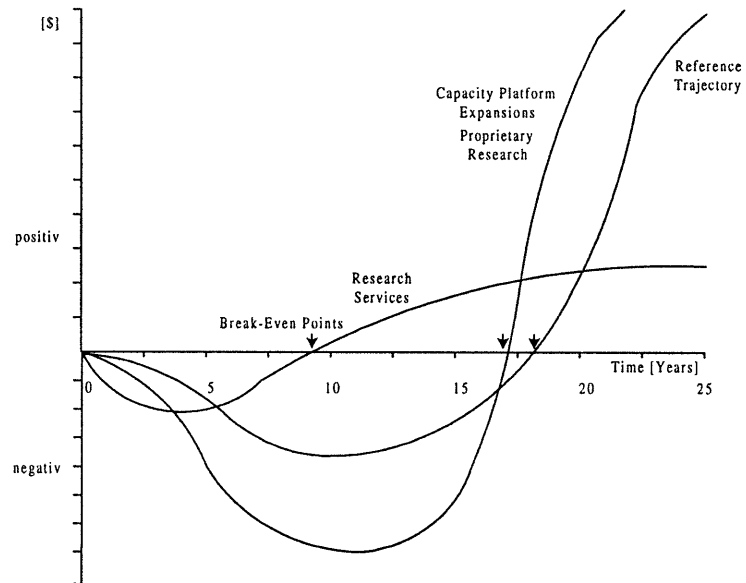
Figure 8 distinguishes between proprietary and collaborative research. This is essential since biotechnology firms receive cash flows only for collaborative research. However, they pay for all discovery activities necessary to advance proprietary projects.

The dynamic consequences from proprietary research are: more strongly increasing rate of cash outflow and, therefore, a larger area under this curve in the short run. But, in the medium and long term, *royalty expectations* are higher. Furthermore, milestone and royalty payments increase in the case of R&D success. This indicates that cash inflow curves rise at a higher rate and, consequently, the break-even point for the CF graph may shift to the left. Since the same dynamic consequences are expected for proprietary research and for technology platform expansions, the CF is collapsed into one graph in Figure 9.

Besides proprietary and collaborative research, another way of utilizing capacity are "research services." This means that biotechnology firms perform research activities on a cost plus basis. The firms receive no claims on milestones and royalties. Such a growth option may ensure that biotechnology companies quickly reach break-even but it severely constrains cash inflows and corporate growth in the long run.[50]

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[50] This is an example of the idiosyncratic nature of complex systems causing different short versus long term consequences of decisions as emphasized on page 25f.

Figure 9: Alternative growth trajectories for CF curves[51]

[S]

Reference
Trajectory

Capacity Platform
Expansions
Proprietary
Research

positiv

Research
Services

Break-Even Points

Time [Years]

0   5   10   15   20   25

negativ

Such growth trajectories represent rather good or best case scenarios. The following three hypotheses discuss potential sources for corporate decline.

[51] Both alternative trajectories assume that research capacity expansions are initially more aggressive than in the reference case. For this reason the CF curve declines more rapidly into the negative domain to distinguish clearly from the reference behavior mode.

2. 3   Dynamic Hypotheses on Corporate Decline

The implicit assumption for previous hypotheses is that biotechnology firms are able to *sustain* a *continuous* flow of research success. To achieve this goal a set of policies is required regarding (a) extent of resource allocation and (b) its purpose (external versus internal development of expertise). Mediocre decision rules lead to discontinuities in research success. This may cause corporate decline and unfavorable external conditions can enforce such a trend.

5. Hypothesis: Lack of continuous research success causes corporate decline and
    unfavorable environmental conditions enforces this trend

Figure 10 depicts the loop set hypothesized.

Figure 10: Dynamic hypothesis on resource allocations
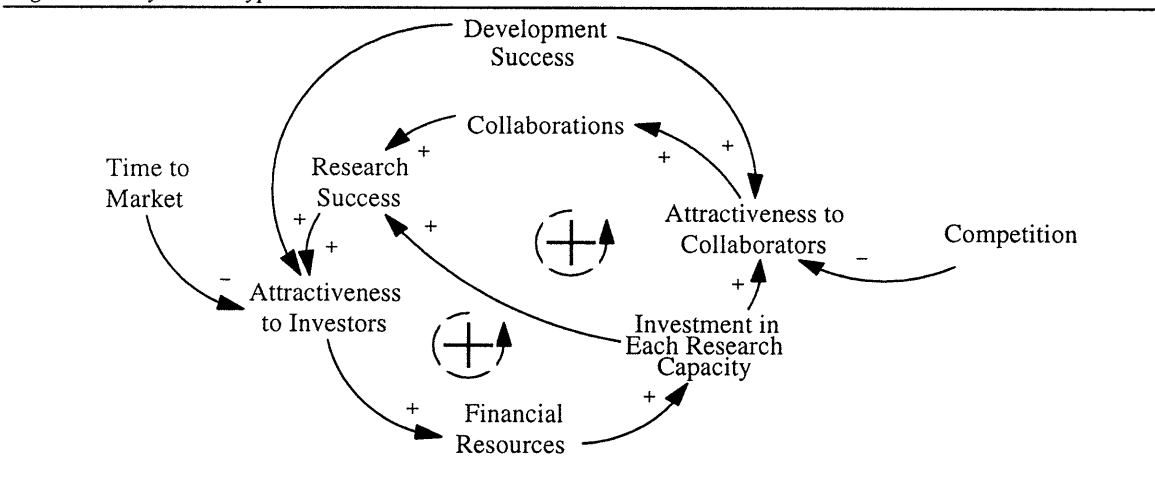
Figure 10 illustrates a link from *investment in each research capacity* and *research success*. This is a proxy for resource allocation policies to perform activities in the drug discovery path. If these rules are mediocre, research success decreases and growth loops turn into vicious circles.

Unfavorable environmental conditions may enforce decline. Figure 10 illustrates three examples which weaken corporate growth:

1. Increasing competition for research collaborations,

2. Decreasing development success, and

3. Increasing time to market.

There are other inherent threats to growth. For instance, the policy of capacity expansion may lead to a platform being too broad to sustain under worsening environmental conditions. This leads to the next dynamic hypothesis on corporate decline.

6. Hypothesis: Technology platforms being to broad cause corporate decline

Figure 11: Hypothesized decline due to "spread-too-thin" effect
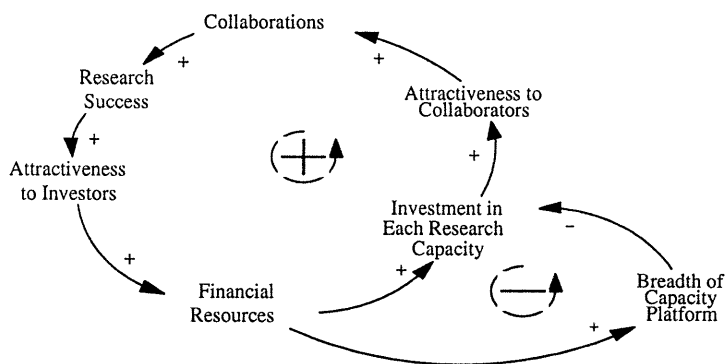
The broader technology platform are the less resources are available for developing each research capacity. By integrating quickly into novel research technologies, the platform may become too broad to be sustained. A "spread-too-thin" effect occurs where no sufficient financial resources are available to maintain a critical mass in each research capacity. Consequently, the attractiveness to collaborators declines.

The last hypothesis is the result of theoretical research rather than derived from discussions with practitioners. It is regarding the risk for investment in pharmaceutical R&D. This risk is measured by the cost of capital concept. A theoretical investigation on

cost of capital, as presented in a later chapter, explains the sources of risk. The theory is validated empirically by a regression model.[52]

The conclusion derived is that future cost burdens cause higher risks for investment in biopharmaceutical companies. It is not the random nature of pharmaceutical research which increases investment risks as usually assumed by R&D practitioners. Technology platform extensions and proprietary research creates future costs. Growth policies in these two areas have, therefore, implications for the risk of investors. This is summarized by the third and last dynamic hypotheses on corporate decline:

7. Hypothesis: Corporate decline caused by future cost burdens

Figure 12 illustrates the hypothesis.

Figure 12: Hypothesized decline due to high cost of capital
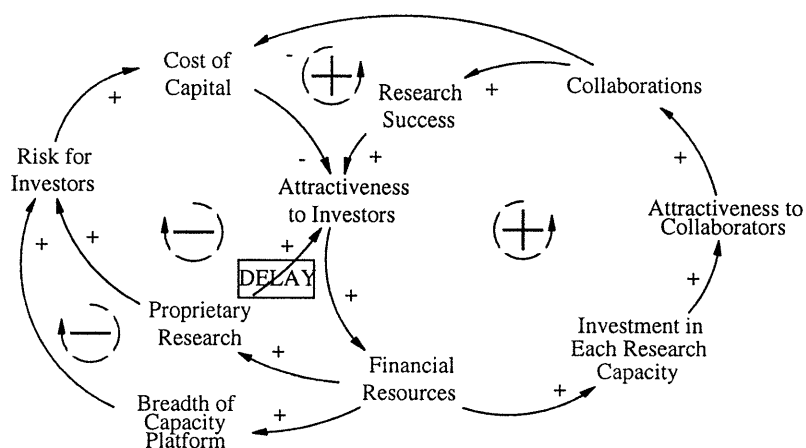
An increasing *Breadth of Capacity Platform* results in additional royalty expectations and therefore the *Attractiveness to Investors* increases. In the Figure above, the delayed effect on investors' attractiveness from proprietary projects is illustrated but not from the breadth of capacity platforms to avoid crossing causal links. Furthermore, only the major loops are labeled.

The two balancing loops represent the impacts of higher risks on *attractiveness to investors*. Decisions such as additional proprietary projects and broader technology

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[52]   See chapter 3.2.

platforms increase future cost burdens. This adds to the risk for investors which leads to higher cost of capital or, stated differently, higher return expectations. Return expectations are compared to actual returns as created by research success.[53] If companies continuously fail to fulfill return expectations, investors loose confidence and the firms' *Attractiveness to Investors* declines. Consequently, the inflow rate of growth capital decreases.

Under such conditions it can be disastrous expanding the technology platform further or going into additional proprietary research. Such growth policies drain scarce cash resources and further increase the cost of capital. Higher cost of capital decreases, ceteris paribus, the firms' attractiveness to investors. This makes it harder to raise additional funds. Furthermore, insufficient cash resources limit a biotechnology company' s ability to react to stronger competition by developing superior research expertise. Lack of expertise results in fewer new collaborations and a reluctance to renew expiring collaborative contracts. Corporate decline and ultimately failure may arise as illustrated by declining arrows in the following Figure 13. However, a change in policies may bring the company back to growth (see the same figure).

Alternatively to proprietary research particularly in start-up and transition phases (Figure 13), biotechnology companies should commit more strongly to collaborative research if possible. This allows to accumulate both cash inflows and research experience. Experience may lead to more drug candidates creating value for investors. Furthermore, collaborative research lowers cost of capital since no future cost are created (see Figure 12).[54] This facilitate access to capital to be invested in proprietary research and technology platform expansions as biotechnology firms move into growth phases (Figure 13). This creates corporate value in the long run.

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[53] Equity investors receive returns from share price appreciation only. No dividends are paid as long as drug candidates are in R&D pipelines.

[54] In other words, average future cost per research project declines.

Such a growth policy analysis is based on insights from feedback loop investigations and they represent general advice. Specific policy design for each phase is only possible with a simulation model.

Figure 13: Potential decline trajectories resulting in failure
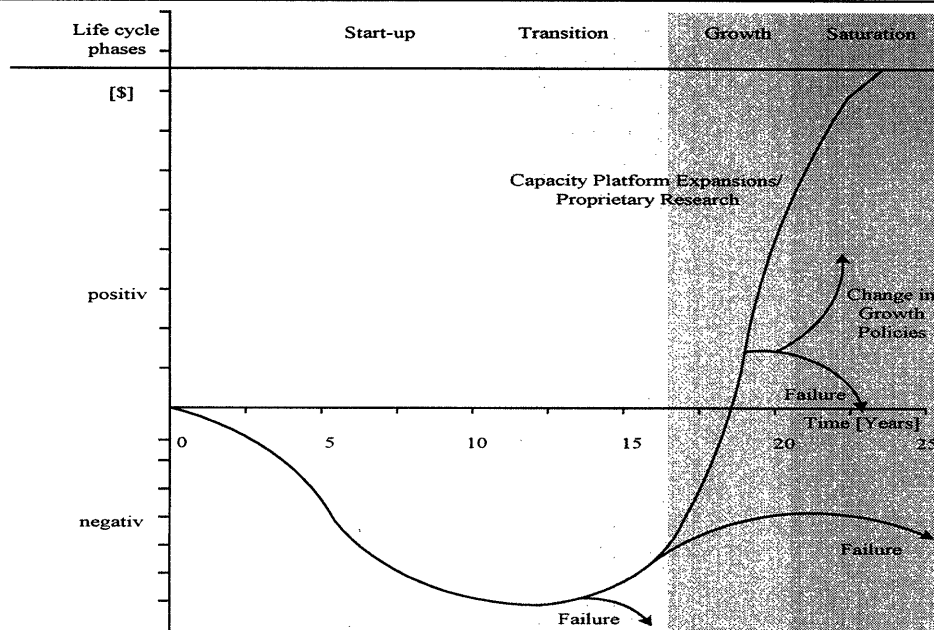
The limits of shaded growth categories are not drawn mathematically where slope changes of the CF curve occur ($\partial^2 CF/\partial t^2 = 0$). They are rather drawn with the loops in mind. The transition phase starts when cash inflows have become strong enough to limit moving into the negative domain. Similarly, the growth phase starts when cash inflow rates strongly outweigh cash outflows and CF increasingly becomes less negative. The saturation phase begins when cash inflows significantly level off.

The following sections present a simulation model constructed for testing these seven hypotheses. The simulation analysis is organized in the following three steps:

1. Replication of those reference growth trajectories presented previously for a fully integrated drug discovery company. Such categories of biotechnology firms develop completely integrated technology platforms over their initial life, specified by assay development, screening, and analoging.[55] The simulation runs are calibrated against data of a real case to increase confidence in the model. This model is then used as an experimentation field for

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[55] Completely or fully integrated means that all activities are performed in-house for discovering drug candidates, which are small molecular weight compounds. Refer to the drug discovery path in the appendix.

2. Sensitivity analyses. By changing policy parameters within a reasonable range consequences on research success and herewith on growth trajectories are observed. This leads to the identification of:

   a. High-impact levers,

   b. Directions of action, i.e., whether to increase or decrease policy levers.

After sensitivity testing, model experiments with different sets of growth policies under various external conditions (strength of competition, etc.) reveal if and when the three hypotheses on corporate decline ultimately cause failure. This analyses is life-cycle phase specific (see top line in Figure 13 for the phases). Based on insights gained in this stage of model experimentation

3. Policies are then designed life-cycle specific with the objective to avoid corporate failure and to sustain growth.

Such policy types are robust in nature. This means that they *ensure* corporate survival even if a set of key conditions worsen within a reasonable range. In addition to worst case scenarios, model experiments are conducted for best and medium cases. Assuming different scenarios, parameter fine tuning has the objective of achieving quasi optimal growth.[56] Fine tuning refers to control interventions such as:

1. The extent of which a high-impact policy lever should be changed,

2. In what combination with other policy levers,

3. The timing of interventions with respect to the phases of corporate life.

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[56] Optimal growth control is impossible for systems of a complexity as the one under investigation. Refer to page 8f.

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3 Appendix

Figure 4: Drug discovery as a sequential chain of research activities
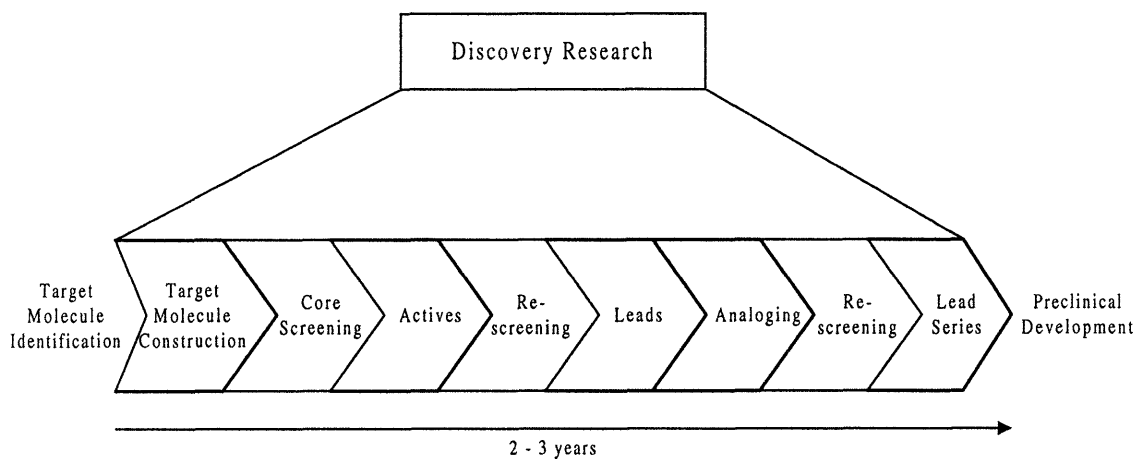
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