The costs of genetic production

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Preliminary draft
For discussion only

Abstract

Longer patents to small inventors may accelerate genetic research with distant payoffs by assuaging their fears that a large, low-cost rival would quickly appropriate profits. [JEL H41, D45]

I. Introduction

Without patents, small firms in biotechnology may be discouraged from innovating by the high fixed costs of research and development. In 1991, biotechnology firms reinvested nearly half of their sales income in R&D; pharmaceutical firms reinvested one-seventh.[2] How can the government design patents to enable small firms to assume the unique costs of designing genes? This note addresses that question.

II. Cost structure in biotechnology

The costs of microscopy may shape the nature of the research project. As the scale of the object of research diminishes to a few nanometers, the cost of research may rise more and more steeply, since a visual image of an object smaller than a nanometer may become prohibitively costly. Research efforts may thus require some guarantee of expected profits that increase as the object size diminishes.

The hourly rental of light microscopes, which provide clear resolutions for objects as small as roughly a quarter of a micrometer in length, may be modest compared to that of electron microscopes, with a power of resolution that is roughly 100 times greater than that of light microscopes. The hourly cost of microscopy, defined as a function with respect to the diminishing size of the object studied, may thus resemble a stepwise function, with one step up occurring at the size of a quarter of a micrometer -- and another, steeper, step at the size of one or two nanometers. The disincentives to innovation, with respect to object size, may thus increase most steeply at a quarter of a micrometer and at about two nanometers. How may patent lengths be designed to maximize the expected value of innovation?

Define the probability of an innovation through genetic research, involving particles of size s, when no patent is granted, as

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[2] Warshofsky (1994).

Equation 1

$$\Pr ob_{NP}[1/s] = \Pr ob_{NP}[x] \geq 0.$$

Equation (8) does not describe a probability distribution, since it does not presume that an innovation at some particle size must occur.

Assume that the probability function follows a stepwise form. To describe the function, denote values. Consider the size of the largest particle that only the light microscope can perceive – that is, the largest particle that the naked eye cannot perceive. Denote this size as $s_{max} = 1/x_2$. Denote the size of the smallest particle that can be seen with the light microscope as $1/x_1$. Provisionally, this particle size is $.25\mu m$. Denote the size of the smallest particle that can be seen with an electron microscope as $1/x_3$, about $2nm$. Then we may specify the function that gives the probability of invention – in a world without patents -- as

Equation 2

$$\Pr ob_{NP}[x] = \begin{Bmatrix} a & x_2 \leq x \leq x_1 \\ b & x_1 \leq x \leq x_3 \\ \leq c & x_3 < x < \infty \end{Bmatrix}.$$

where $c < b < a$. The subscript *NP* denotes "no patenting."

Express the innovator's expectation of net value from an innovation springing from particles of size $s = 1/x$ to be $V(x) \geq 0$, where $V'(x) > 0$ and $V''(x) > 0$. The sign of the second derivative stems from the speculation that the study of smaller particles may lead to major discoveries. For example, only the electron microscope can detect viruses.[3]

A longer patent will encourage the researcher to take on more valuable, though riskier, projects. Lengthening the patent may thus raise the probability of invention – but at a diminishing rate, since the market for the patented product may eventually mature, throttling future profits.

With a patent of length L, the probability of an innovation, estimated by the researcher, is $Prob_P[x,L]$, where

$$0 \leq \Pr ob_P[x, L(x)] \leq 1,$$

$$\frac{\partial \Pr ob_P[x, L(x)]}{\partial x} < 0, \quad \frac{\partial \Pr ob^2{}_P[x, L(x)]}{\partial x \partial x} > 0,$$

$$\frac{\partial \Pr ob_P[x, L(x)]}{\partial L(x)} > 0, \frac{\partial \Pr ob_P{}^2[x, L(x)]}{\partial L \, \partial L} < 0.$$

$$\frac{\partial \Pr ob_P{}^2[x, L(x)]}{\partial x \, \partial L} > 0.$$

[3] Totora, Funke and Case, page 17. A larger x connotes a smaller particle.

The subscript *P* denotes "patenting."

The positive cross-derivative assumes that, for smaller particles, inherent profits in genetic innovations are more likely to be larger in distant years; for, the innovations are likely to be more radical and thus eventually to incur larger spin-off profits. Thus, as the particle studied diminishes in size, a slight lengthening of the patent will increase expected profits by much more.

Policymakers now consider the lengths of genetic patents to grant, as a function of the scale of particle studied. They choose the length function *L(x)*, under the constraint that the sum of patent years to any one inventor cannot exceed *R*, perhaps because policymakers wish to limit the accumulation of market power in genetic production. For example, under the Organ Drug Act of 1983, the developer of a drug for treating rare diseases that affect 200,000 people or fewer receives no more than seven years of patent exclusivity.[4] Denote the probability of an innovation for a particle of size $s = 1/x$ without a patent – in effect, for a patent of length 0 – as $Prob_P[x,0]$. Then, in a world with patents, the policymaker chooses *L(x)* to maximize the expectation of net value of genetic innovations:

$$\int_{x_2}^{x_1} \left(\Pr ob_P[x, L(x)] - a\right) V(x)\, dx + \int_{x_1}^{x_3} \left(\Pr ob_P[x, L(x)] - b\right) V(x)\, dx + \int_{x_3}^{\infty} \left(\Pr ob_P[x, L(x)] - c\right) V(x)\, dx + \lambda_1 \left[R - \int_{x_2}^{\infty} L(x)\, dx \right]$$

The first-order conditions yield

Equation 3

$$\frac{\partial \Pr ob_P[x, L(x)]}{\partial L(x)} V(x) - \lambda_1 \leq 0, \quad x_2 \leq x < \infty,$$

$$R - \int_{x_1}^{\infty} L(x)\, dx \geq 0.$$

The first condition in (3) suggests that policymakers should set patent lengths so that the expectation of net value is the same for each particle size at the margin, with respect to the length of the patent. This condition connotes longer patents for smaller particles, essentially because those patents are worth more. The reasoning is this: As the particle size shrinks, the value *V* of an innovation rises. Since, by the first of the first-order conditions, the expectation of net value is λ_1 for every particle size, a larger *V* implies a smaller marginal probability with respect to patent length. Since the second

[4] Warshofsky (1994).

derivative of the probability function with respect to patent length is negative, a smaller marginal probability implies that a longer patent is optimal for the smaller particle.

Regardless of the type of microscope used, fixed development costs may also rise with the number of chromosomes in the genome studied. In creating a gene, researchers often must first determine where a natural gene with a similar function lies on the chromosomes. One method, somatic cell hybridization, melds the nucleus of a cell of the target species with the nucleus from a faster-growing species – creating, for example, a hybrid of human and mouse cells. As clones of the hybrid cell grow, they eventually lose some human chromosomes. An offshoot thus eventually contains fewer chromosomes than the parent hybrid cell, although a given chromosome may appear in more than one offshoot. Researchers can then attempt to combine, with each offshoot run, a clone of a given gene. The matching can determine which chromosome holds the gene.[5]

Let an "experiment" be a trial that focuses on a chromosome. When chromosomes are many, the researcher may expect that she may need to run many experiments to identify the chromosome of a given gene. Thus the planned number of runs, k, may rise with the genome's number of chromosomes, M. Consider now the probability, from experiment to experiment, of identifying the right chromosome. The first experiment randomly targets one of M chromosomes. The probability that this chromosome contains the gene is $1/M$. The probability that the second experiment would target the right chromosome is the probability of reaching the second experiment ($[M-1]/M$) times the probability that this experiment's chromosome contains the gene ($1/[M-1]$). Similar arguments apply to experiments 3 through k. The minimum probability of identifying the chromosome in k runs is thus

$$\frac{1}{M}+\frac{M-1}{M}\frac{1}{M-1}+\frac{M-1}{M}\frac{M-2}{M-1}\frac{1}{M-2}+\ldots$$
$$+\frac{M-1}{M}\frac{M-2}{M-1}\frac{M-3}{M-2}\ldots\frac{M-(k-1)}{M-(k-2)}\frac{1}{M-(k-1)},$$

or

Equation 4

$$\frac{k}{M}.$$

Since the relevant chromosome may occur in several runs, the actual probability of identifying it in k runs may be greater than indicated in (4).[6]

We may now consider the expected cost of a sequence of runs to determine the location of the gene. Suppose that a run costs c. Also suppose that the researcher will

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[5] Cooper, pp. 162-165.

[6] A larger hybrid nucleus may hold more human chromosomes. One may speculate that the actual probability may depend on the size of the nucleus in the offshoot hybrid cell, relative to that of the parent cell.

choose the expected number of runs and that each run is independent of the others. Then we may express an expectation of the cost of a sequence as

Equation 5

$$EC(M) = c\sum_{k=1}^{M} p(k)k = c\sum_{k=1}^{M} \frac{k}{M}k.$$

In this formula, (5), the probability *p(k)* of determining the chromosome in *k* runs sums several probabilities: That of determining the chromosome in the first run; to that of determining it in the second run, conditional on not determining it in the first run; and so forth. The probabilities thus do not attach to events that are so defined that exactly one must occur; for example, identifying the correct chromosome might require more than *k* runs. One should not interpret (5) as an expected value in the conventional sense that the probabilities sum to 1. Instead, one might interpret it as a practical shortcut to estimating the cost of using somatic cell hybridization.

From (5), the marginal expectation of the cost of the technique, with respect to the number of chromosomes *M* in the genome studied, is

$$\begin{aligned} MEC(M) &= \frac{\partial EC[M]}{\partial M} = cM - \frac{c}{M^2}\sum_{k=1}^{M} k^2 \\ &= cM - \frac{c}{M^2}\left[\frac{M(M+1)(2M+1)}{6}\right] \\ &= cM\left[\frac{2}{3} - \frac{1}{2M} - \frac{1}{6M^2}\right]. \end{aligned}$$

The marginal expectation of cost is positive for $M > 1$, and it rises about linearly as *M* increases.[7] If one accepts this way of thinking about the expectation of cost, then one may also anticipate that granting a longer patent may be more efficient in the study of larger genomes.

Nonconvexities in the production of genetic material may make longer patents more valuable to the small inventor, since she may otherwise face a large rival who can finance research from the profits accumulated over declining marginal costs. Several methods of producing genetic material may incur scale economies. In some cases, these economies occur with respect to time. The polymerase chain reaction, for example,

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[7] The derivative of marginal expected cost with respect to the number of chromosomes is

$$\frac{\partial MEC}{\partial M} = \frac{1}{M}\left[MEC + c\left(\frac{1}{2} + \frac{1}{3M}\right)\right].$$

With MEC about equal to $kM + b$, the expression goes to $k + c/2$ as *M* becomes large.

doubles the amount of genetic material produced at each stage.[8] In other cases, a capital input generates falling marginal costs. In electroporation, one electric current courses through many cells stripped of their walls; the electricity punches pores into the cells so that DNA can be inserted through their membranes. Researchers may instead prepare cells to take up DNA from the outside by soaking them *en masse* in calcium chloride; the technique seems likely to lower labor costs at the margin as production increases.

Some ways of producing genetic material, however, may incur constant costs. In microinjection, researchers insert DNA into a cell through a small glass pipe; the unit cost of such an injection may remain the same for large batches as well as for small.

Generally, the nature of fixed costs in production may depend partly on how researchers inject the genetic material into an instrument for its mass production. They may first inject it into a vector phage or into a circular molecule (i.e., a plasmid), perhaps based on the bacterial virus ë. The phage or plasmid may then be injected into a cell that reproduces rapidly, such as an *E. coli* bacterium.

The method of injection may also affect the probability of successful duplication. Consider the probability that the nucleus of the cell takes up, for example, part of a foreign DNA strand. This probability may vary with the method used to inject the strand. For example, one may speculate that the probability may be higher if the material is injected directly into the nucleus than if it is packed into a liposome that first melds with the plasma membrane of the cell. The fixed production cost may vary inversely with this probability.

III. Conclusions

Dominant technologies for reproducing genetic material – particularly cloning -- seem nonconvex. Longer or more lenient patents to small inventors may thus accelerate research by dispelling their fears of being usurped by a large producer.

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[8] Tortora, Funke and Case, 1995.