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R&D investments for neglected diseases can be sensitive to the economic goal of pharmaceutical companies

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A fundamental problem with neglected diseases is how to induce pharmaceutical companies to invest resources for developing effective treatments. A recent debate focused on the role of economic incentives represented by monetary transfers to the firms. In this article I focus on the economic goals of pharmaceutical companies, as determinants for R&D effort. In particular, within a stylized framework, the work compares expected profit and expected productivity maximization, arguing that the former in general induces higher R&D investments than the latter. Therefore, as it is currently the case, when pharmaceutical firms focus on productivity, appropriate economic incentives might be needed for them to invest in R&D for neglected diseases.

A fundamental problem with infectious and tropical diseases is how to induce pharmaceutical companies to invest resources for developing drugs treating such diseases. The issue arises because most of these diseases affect poor components of the world population, which implies that although the potential demand for such drugs is large its market value is low because those affected cannot pay for medications. For this reason in recent years an intense debate has taken place on the appropriate economic drivers to induce pharmaceutical firms to invest in R&D to develop treatments for such diseases. The debate largely focused on the role of economic incentives as represented by monetary transfers to pharmaceutical firms, and [1–4; The right Tool(s): Designing Cost-Effective Strategies for Neglected Disease Research: http://www.who.int/intellectualproperty/studies/S.Maurer.pdf] offer a broad perspective on the main issues at stake in the discussion.

In this article I consider a complementary direction by discussing to what extent, if at all, even when transfers from outside are scarce or not available to a company, there could still be room for economic considerations to enhance R&D. More specifically, I focus attention on the economic goal pursued by pharmaceutical companies, because the strength of monetary transfers might vary across different objectives that firms are trying to achieve [6].

In deciding how much to invest typically companies are assumed to be concerned about expected profits, because it is hard to imagine firms remaining in business without a proper account for profits. Yet other economic considerations such as market share, or revenue maximization might prevail at times. For example, in recent years the pharmaceutical industry has put particular emphasis on catching up with productivity decline [5–7]. Building on insights in article [8], concerning the optimal portfolio composition of pharmaceutical compounds under development, the paper compares R&D effort when firms are concerned about profits with respect to productivity. The framework considers a representative company which means that the main findings hold in general, that is whether or not a disease is neglected. Hence in my stylized model, neglected diseases can be characterized precisely for what they are, that is, diseases with particularly low future revenues.

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It is standard to formalize profit-driven behavior with companies maximizing their expected profits (EP) while maximization of a simple indicator such as the expected rate of return (ERR) (average expected profit) could well capture concern for productivity [8; Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products: http://www.fda.gov/oc/initiatives/criticalpath/]. The difference underlying the two is simple.

While EP maximization is based on the idea of 'total' profitability of the investments, where the target is the overall cash flow, ERR maximization is based on the idea of 'relative' profitability, more specifically profitability per monetary unit invested. Therefore, ERR is adopted when firms take the prevailing market interest rate as reference for setting their economic priorities. In this article I compare these two profit-based goals as drivers for R&D effort, and which of them is adopted typically depends on the view that managers have of their companies in different economic scenarios. However, the main point of this article is to discuss that, although closely related, maximization of EP and ERR might not necessarily lead to the same R&D investment level. More specifically, based on a stylized model I argue how EP maximization might induce a less conservative R&D investment behavior than ERR maximization, with a key role for this being played by the nature of the discovery process. Broadly speaking, for ERR maximization to induce positive R&D investment a necessary, although not sufficient, condition is that the discovery process should be sufficiently 'easy', where the 'degree of difficulty' will be made precise through the notion of success probability returns from R&D investment. This means that the investment level of pharmaceutical firms would be sensitive not only to the availability of monetary transfers from outside, but also to the economic goal they pursue.

Therefore the negative effect on the R&D investment level of a market with weak or no economic value, such as the market for drugs treating NDs, could be further exacerbated or partially countervailed depending upon the economic goal chosen by companies.

The notion of returns from R&D investments in drug discovery success probability

Whether a process of drug discovery would eventually be successful is inherently uncertain. However, different processes might have different degrees of difficulty and, so, of uncertainty associated to their possible success. In this section the degree of difficulty of a drug discovery process will be formalized by the nature of its success probability. To make this more precise I need to introduce some notation. If C is the amount of R&D monetary investment chosen by a firm, with $p(C)$ I indicate the probability of successful drug discovery, as a function of C. The way $p(C)$ changes as C varies describes how, 'difficult' or 'easy', the discovery process is perceived to be by the firm. Note that launching a new molecule requires about US$873 millions in R&D investments [6]. Taking this amount as the current reference for registering a new drug, we would interpret a lower level of R&D effort as inducing, on average, less than one registered drug.

Throughout this article I assume $p(0) = 0$, namely that successful drug discovery is impossible with no R&D effort. Moreover to simplify the exposition, but with no major loss of generality, I assume $p(C)$ to be a continuous, differentiable, function of C, and that $p'(C) > 0$ over the relevant R&D effort levels, that is $p(C)$ increases with C.

However, in view of the current situation with the pharmaceutical industry, which appears to suggest that success probability might not always increase with R&D investments [7], below I shall also discuss the case of $p'(C) \leq 0$.

If a $p(C)$ which increases with C it is likely to characterize most drug discovery processes, then a further important feature of the success probability function, namely the rate at which $p(C)$ increases with C, is going to have a major role for the firm decision on how much to invest in R&D. The $p(C)$ rate of growth is what formalizes its returns from R&D investments. In particular, returns from R&D investments could be of three types: (i) decreasing returns, (ii) constant returns, (iii) increasing returns. A probability function $p(C)$ exhibits 'decreasing returns' from R&D if its growth rate decreases with C. Formally this translates into $p'(C)$ decreasing with C, namely into $p''(C) < 0$. 'Constant returns' imply $p''(C) = 0$ while 'increasing returns' $p''(C) > 0$. Finally still to simplify the exposition, without losing much in generality, we assume that the available R&D budget B for a firm is large enough so as to cover any investment decision.

A numerical example

Before going through some more formal analysis it is worth illustrating the three types of returns by means of a simple numerical example, summarized in Table 1.

Considering as an example three possible R&D investment levels, $C = 200, 400, 800$, where each positive investment is twice as large as the previous one, Table 1 illustrates that as C doubles decreasing returns obtain when the success probability less than doubles its value, constant returns when $p(C)$ doubles and increasing returns when $p(C)$ more than doubles.

Decreasing returns from R&D investments

Because of decreasing returns it is $p''(C) < 0$, which also implies $p'(C) < p(C)/C$, namely that the marginal increase in the success probability is lower than the average probability for all C. Moreover, to define EP and ERR we need to introduce the prospective future profits $R = \mathcal{R} - \mathcal{C}$, namely the revenues $\mathcal{R}$ that will accrue to the firm conditional on successful drug discovery, minus the drug production and distribution costs $\mathcal{C}$.

Maximization of expected profits

Given the above assumptions and notation I now consider a pharmaceutical company maximizing its expected profits $E\Pi(C)$ that is a firm solving the following problem:

$$Max_c E\Pi(C) = Max_c(\, p(C)R - C) \qquad (1)$$

where $E\Pi(C)$ is expressed in monetary units, clearly $E\Pi(0) = 0$. Moreover, it is simple to check that the optimal R&D level $C = C_{EP}$ in this case will be:

$$\begin{cases} C_{EP} > 0 & \text{if } \; p'(0)R - 1 > 0 \\ C_{EP} = 0 & \text{otherwise} \end{cases} \qquad (2)$$

In other words for a firm to have a positive EP, and so to invest a positive amount of resources in R&D, the success probability function should be 'steep enough' at low investment levels, where how steep will be determined by future profits. The higher the value of R, the more attractive the project, and the less steep $p(C)$ needs to be. Therefore if R is sufficiently low, that is the relevant market has little or no economic

TABLE 1

Success probability returns[a]

	Decreasing returns	Constant returns	Increasing returns
C = 200	$p(C) = \frac{1}{2}$	$p(C) = \frac{1}{4}$	$p(C) = \frac{1}{10}$
C = 400	$p(C) = \frac{3}{4}$	$p(C) = \frac{1}{2}$	$p(C) = \frac{2}{5}$
C = 800	$p(C) = 1$	$p(C) = 1$	$p(C) = 1$

[a] The values of C are in $\$m$ln.

potential, the company might decide not to invest in R&D and, consistently with the main current view, the disease would remain neglected. If the firm finds it optimal to choose positive R&D then C_{EP} will be determined by the following optimality condition:

$$\frac{dE\Pi(C)}{dC} = p'(C_{EP})R - 1 = 0 \Rightarrow p'(C_{EP}) = \frac{1}{R} \quad (3)$$

Because of the assumptions on $p(C)$ condition (3) suggests that the larger the value of R, the lower $p'(C_{EP})$ and the greater the R&D investment level C_{EP}. For a better understanding of the above discussion, suppose $p(C, a) = 1 - e^{-aC}$, where $a > 0$ is a parameter formalizing the intrinsic difficulty of the discovery process. It is simple to check that the second derivative of $p(C, a)$ with respect to C is negative, and so that returns from R&D are decreasing. Moreover, because $dp(C, a)/da = Ce^{-aC} > 0$, the larger is the value of a the easier is discovery. Moreover, because $dp(C, a)/dC = ae^{-aC}$ then $p'(C = 0, a) = a$. Hence condition (2) becomes $a > 1/R$ while from Eqn (3) we obtain that $C_{EP} = \log(aR)/a$ which is positive, because $Ra > 1$, and increasing in R as well as decreasing in a, for $a > e/R$. The example captures a discovery process where the R&D effort is maximum when its intrinsic difficulty is neither too high, not too small.

Maximization of expected rate of return

Now consider a pharmaceutical firm maximizing its expected rate of return $E\rho(C)$, by solving the following problem:

$$Max_C E\rho(C) = Max_c \frac{E\Pi(C)}{C} = Max_c \frac{p(C)R - C}{C} \quad (4)$$

By solving problem (4) it follows that $E\rho(C) \geq 0$ under the same condition as specified in (2), provided we define

$$Lim_{C \to 0} E\rho(C) = E\rho(0) = p'(0)R - 1 \quad (4a)$$

It is worth noting that based on the argument that when $C = 0$ no productivity could materialize then a more realistic assumption than Eqn (4a) could perhaps be the following:

$$E\rho(0) = 0 \quad (4b)$$

In this case the function $E\rho(C)$ might not have a maximum but the main underlying message would basically be unaltered.

Differentiating the expected rate of return to solve (4) we obtain

$$\frac{dE\rho(C)}{dC} = \frac{(p'(C)R - 1)C - (p(C)R - C)}{C^2} = \frac{R(p'(C)C - p(C))}{C^2} \quad (5)$$

and since $p''(C) < 0$ implies $p'(C) < p(C)/C$ then $dE\rho(C)/dC \leq 0$ for all $C \geq 0$, that is ERR decreases with C. It follows that if ERR could at all be positive, then the optimal R&D investment level is $C_{ERR} = 0$, and the maximum level attainable by ERR in this case is given by $E\rho(0) = p'(0)R - 1$. If $E\rho(0) = 0$ then $E\rho(C)$ would decrease but only for $C > 0$. For this reason it would be still be optimal to invest as little as possible in R&D, however as long as $C > 0$.

Although based on a stylized model, the above analysis provides some interesting insights. In summary:

(i) Even if the conditions for positive EP and positive ERR are the same, when a company maximizes EP, it will find it optimal to choose a positive R&D investment whereas when it maximizes ERR would prefer not to invest in R&D.

(ii) When EP and ERR are both positive, while Eqn (3) suggests that with EP maximization the optimal R&D investment depends on the prospective profits R, from expression (5) instead it follows that when ERR is maximized the optimal R&D effort has nothing to do with the economic component R but depends only on the shape of $p(C)$. This might have some important bearings from expression (5) instead it follows while economic incentives enhancing R, in the form of a given sum of money transferred to the firm, would tend to increase R&D investments under EP maximization, they might have little or no effect on R&D when ERR is maximized.

With ERR maximization there is a very small, or no, R&D investment, this is an admittedly drastic conclusion, however crucially driven by the assumption of decreasing returns. Therefore it is interesting to see whether the same, or similar, conclusions, would hold when returns from R&D effort are not decreasing. Table 2 presents a numerical illustration of the main findings. Table 2 illustrates that, with decreasing returns, although expected profits are maximized at $C = 400$ expected productivity is maximized at the lowest level $C = 200$.

TABLE 2

Decreasing returns from R&D investments[a]

	$p(C)$	R	$E\Pi(C) = p(C)R - C$	$E\rho(C) = \frac{E\Pi(C) = p(C)R - C}{C}$
C = 200	$\frac{1}{2}$	1000	300	$\frac{300}{200} = \frac{3}{2}$
C = 400	$\frac{3}{4}$	1000	350	$\frac{350}{400} = \frac{7}{8}$
C = 800	1	1000	200	$\frac{200}{800} = \frac{1}{4}$

[a] The values of C and R are in $\$m$ln.

Constant returns from R&D investments

Constant returns of scale imply $p''(C) = 0$ and the success probability equal to $p(C) = aC$, with $a > 0$ and $0 \leq C \leq 1/a$ where, $a > 0$ is a parameter formalizing the degree of intrinsic difficulty of the discovery process. Again, the higher the value of a the easier the discovery process. Alternatively, we could define $p(C) = \min\{1, aC\}$, for all $C \geq 0$, leaving the main content of the assumption unaltered.

In this case $p'(C) = a = p(C)/C$ namely marginal and average probabilities are the same, at any investment level $C \leq 1/a$.

Maximization of expected profits

Since now

$$E\Pi(C) = aCR - C = C(aR - 1) \quad (6)$$

then if $aR - 1 > 0$, that is if as in the previous example $a > 1/R$, EP would be positive and the optimal R&D level would now coincide with the highest possible investment, given by $C_{EP} = 1/a$. Note that in this case R would have a role only in so far as whether to invest but not how much to invest. Moreover, since $R > 1/a$ in this case $R > C_{EP}$ and the company expected profit would be equal to $E\Pi(C_{EP}) = R - (1/a)$.

Alternatively, if $a = 1/R$ then expected profits would be zero and any R&D investment level optimal. Finally, if $a < 1/R$ expected profits would be negative and $C = 0$ optimal.

Maximization of expected rate of return

In this case

$$E\rho(C) = \frac{aCR - C}{C} = aR - 1 \quad (7)$$

for $C \geq 0$ suggesting that, with constant returns, ERR is positive under the same condition as for EP. However, unlike EP, ERR is constant and independent of C. It follows that a

TABLE 3

Constant returns from R&D investments[a]

	$p(C)$	R	$E\Pi(C) = p(C)R - C$	$E\rho(C) = \frac{E\Pi(C) = p(C)R - C}{C}$
$C = 200$	$\frac{1}{4}$	1000	50	$\frac{50}{200} = \frac{1}{4}$
$C = 400$	$\frac{1}{2}$	1000	100	$\frac{100}{400} = \frac{1}{4}$
$C = 800$	1	1000	200	$\frac{200}{800} = \frac{1}{4}$

[a] The values of C and R are in $\$m$ln.

change in returns on R&D effort can now make ERR maximization compatible with any level of investment in the relevant range $0 \leq C \leq 1/a$. Analogous considerations as in the previous paragraph would hold for non-positive profits.

Unlike Table 2, Table 3 illustrates that although expected profits are maximized at $C = 800$, expected productivity is maximized at any level C.

Increasing returns from R&D investments

I now discuss increasing returns. In this case $p''(C) > 0$ over the interval $0 \leq C \leq C^*$, where C^* is such that $p(C^*) = 1$.

Maximization of expected profits

Because $p''(C) > 0$ the first order condition (3) would now identify the R&D effort level minimizing, rather than maximizing EP. In fact, it is either $C_{EP} = 0$ or $C_{EP} = C^*$.

Maximization of expected rate of return (ERR)

Considering Eqn (5) again we now notice that $p''(C) > 0$ implies $p'(C) > p(C)/C$, and so $dE\rho(C)/dC > 0$, namely ERR is strictly increasing in C, and it is simple to check that EER and EP would induce the same positive R&D effort level.

Some robustness checks and extensions

In this section I am going to enquire how robust the previous findings are with respect to alternative formulations of the main assumptions, as well as extensions of the basic framework.

An alternative formulation of the expected rate of return

In this paragraph I perform a first, simple, robustness check of the above results by considering a different formulation of ERR, in which expected profits will be averaged out by the sum of R&D and prospective production and distribution costs $\mathcal{C}$, that of course will be paid only upon successful discovery, namely with probability $p(C)$. This modified version of the expected rate of return $E\rho^*(C)$ is now defined as

$$E\rho^*(C) = \frac{p(C)R - C}{C + p(C)\mathcal{C}} \tag{8}$$

Differentiating $E\rho^*(C)$ we obtain

$$\frac{dE\rho^*(C)}{dC} = \frac{(p'(C)R - 1)(C + p(C)\mathcal{C}) - (p(C)R - C)(1 + p'(C)\mathcal{C})}{(C + p(C)\mathcal{C})^2} = \frac{(R + \mathcal{C})(p'(C)C - p(C))}{(C + p(C)\mathcal{C})^2} \tag{9}$$

whose sign is again fully determined by the sign of $p'(C)C - p(C)$, which means that $E\rho^*(C)$ is maximized under the same conditions as $E\rho(C)$. This suggests the previous findings to be relatively robust with respect to the definition of ERR.

Generalizing the probability function p(C)

In view of the current situation in the pharmaceutical industry, where the success probability does not seem to increase with R&D investments, here I briefly investigate the implications of a $p(C)$ which might not always increase. For the sake of the exposition, I will start discussing a simple case and then extend its main findings. Moreover, in what follows I consider expected profit maximization, since similar considerations will hold for productivity.

Clearly the extreme case of $p'(C) < 0$, for all $C \geq 0$, would not be interesting since expected profits could never be positive and $C = 0$ optimal. Therefore, suppose instead that $p'(C) > 0$ for $0 < C < \bar{C}$, $p'(\bar{C}) = 0$ and $p'(C) < 0$ for $\bar{C} < C$. This would capture an, admittedly, extreme case of decreasing returns where an increase in R&D investments enhances success probability but only up to a certain level $C = \bar{C}$, after which they would produce negative effects on success. Although the conditions for positive investments, $p'(0)R - 1 > 0$, and optimality $p'(C_{EP}) = 1/R$ remain unaltered in this case, the following observation which would not pertain the case of $p'(C) > 0$ can now be made. From $p'(\bar{C}) = 0$ it follows that the first derivative of the expected profit at $C = \bar{C}$, that is where the probability function reaches its maximum, being given by

$$p'(\bar{C})R - 1 = -1 < 0$$

is negative. Therefore, because of the above assumptions, the optimality condition $p'(C_{EP}) = 1/R$ implies that $p'(C_{EP}) > 0$ and so that $C_{EP} < \bar{C}$. In other words, R&D investments would not maximize success probability and companies, in this sense, would under invest with respect to the optimal probabilistic level $\bar{C}$, although as R gets large C_{EP} would approach $\bar{C}$. Thus, $\bar{C}$ acts as an upper bound to the level of investments, because the company would never find it profitable to choose C on an interval where $p(C)$ is decreasing.

It is easy to check that this last consideration extends as follows:

Conclusion 1: If profits can be positive, and $p(C)$ differentiable for all, C then it cannot be $p'(C_{EP}) \leq 0$.

Intuitively, the above conclusion suggests that is never optimal for a company to choose an R&D profit maximizing investment level where success probability does not increase. Therefore it would be optimal to select either a lower, or a higher, level of investment.

Economies of scope: a portfolio of compounds

To take account of the fact that pharmaceutical firms typically develop more than one compound at the same time, in this paragraph I extend the basic framework to more than one project. To illustrate the issue we consider two compounds, bearing in mind that similar considerations extend to any number of molecules.

Suppose a firm considers to develop two molecules, $i = 1, 2$. By C_1 we indicate the R&D investment in compound $i = 1$, with success probability $p_1(C_1)$ and net future return R_1. Similarly, C_2 is the R&D investment in compound $i = 2$, $p_2(C_2)$ its success probability R_2 and its net future return. We assume the two projects to be independent, that is the probability that both compounds will be registered is $p_1(C_1)p_2(C_2)$

Therefore, the levels of C_1 and C_2 maximizing the expected profit $E\Pi_P(C_1, C_2)$ of the whole portfolio solve

$$Max_{C_1,C_2} E\Pi_P(C_1,C_2) = Max_{C_1,C_2}[p_1(C_1)R_1 - C_1] + [p_2(C_2)R_2 - C_2] \quad (10)$$

while those maximizing the expected profit $E\Pi_i(C_i)$. of the single projects solve

$$Max_{C_i} E\Pi_i(C_i) = Max_{C_i}\, p_i(C_i)R_i - C_i \quad (11)$$

If $C_i^{\Pi_P}$ and $C_i^{\Pi_i}$ solve, respectively, problems (10) and (11) for molecule i then, because of additivity of problem (10) it follows immediately that $C_i^{\Pi_P} = C_i^{\Pi_i}$.

Analogously, the R&D investment levels maximizing the expected productivity $E\rho_P(C_1, C_2)$ of the portfolio solve

$$Max_{C_1,C_2} E\rho_P(C_1,C_2) = Max_{C_1,C_2} \frac{[p_1(C_1)R_1 - C_1] + [p_2(C_2)R_2 - C_2]}{(C_1 + C_2)} \quad (12)$$

Suppose C_i^{ρ} solve problem (12) for molecule i and rewrite $E\rho_P(C_1, C_2)$ as

$$E\rho_P(C_1,C_2) = \frac{[p_1(C_1)R_1 - C_1]}{(C_1 + C_2)} + \frac{[p_2(C_2)R_2 - C_2]}{(C_1 + C_2)} \quad (13)$$

Then, for given C_2, it follows immediately that the term $[p_1(C_1)R_1 - C_1]/(C_1 + C_2)$ cannot be maximized by a C_1 larger than $C_1^{\Pi_1}$ since $C_1 = C_1^{\Pi_1}$ would increase the numerator and decrease the denominator, of $[p_2(C_2)R_2 - C_2]/(C_1 + C_2)$ too. A similar reasoning holds for molecule $i = 2$ leading to the conclusion that the portfolio R&D effort with expected productivity maximization, $C_1^{\rho} + C_2^{\rho}$, is never higher than the portfolio investments with expected profit maximization $C_1^{\Pi_1} + C_2^{\Pi_2}$.

Developing a portfolio with several molecules exhibits a concern for economies of scope [9]. An interesting, recent, example for linking explicitly economies of scope to NDs is given by the so-called, priority review vouchers [10–12].

Competition

In this paragraph I briefly discuss the possibility that drug discovery processes, requiring relatively limited R&D investments, could attract more than one firm in the relevant market, sharing the available revenues. I am interested in investigating if the presence of multiple firms can affect the overall R&D effort. To gain some initial insights I consider a duopoly, where firms maximize expected profit and returns from R&D are decreasing.

Suppose an R&D process is sufficiently 'easy' to enable two firms, $i = 1, 2$, to afford investing in the market and obtain positive profits. For simplicity suppose both firms adopt the same technology, that is they have the same success probability $p(C_i)$. Market revenues are given by R: hence, if both companies succeed they will share R equally whereas if only one firm will succeed it will enjoy the entire market revenue. Therefore the profit function of firm $i = 1$, and analogously for firm $i = 2$, is defined by

$$\Pi_1(C_1,C_2) = \begin{cases} \frac{R}{2} - C_1 & \text{with probability } p(C_1)\,p(C_2) \\ R - C_1 & \text{with probability } p(C_1)(1 - p(C_2)) \\ -C_1 & \text{with probability } 1 - p(C_1) \end{cases} \quad (14)$$

From Eqn (14) it follows that its expected profit would be given by

$$E\Pi_1(C_1,C_2) = \left(\frac{R}{2} - C_1\right) p(C_1)\,p(C_2) + (R - C_1)\,p(C_1)(1 - p(C_2)) - C_1$$

which rearranged, leads to

$$E\Pi_1(C_1,C_2) = p(C_1)R - p(C_1)\,p(C_2)\frac{R}{2} - C_1 \quad (15)$$

Analogously, the expected profit of firm $i = 2$ would be

$$E\Pi_2(C_1,C_2) = p(C_2)R - p(C_2)\,p(C_1)\frac{R}{2} - C_2 \quad (16)$$

It is easy to check that now expected profits can be positive for firm $i = 1$ (and similarly for firm $i = 2$) if

$$p'(0)(1 - p(C_2)/2)R - 1 > 0$$

which consistently with the intuition, is more restrictive for $p'(0)$ than when only one firm is in the market. Differentiating Eqn (15) the C_1 expected profits maximizing level solves

$$p'(C_1)(2 - p(C_2)) = \frac{2}{R} \quad (17)$$

while C_2 solving

$$p'(C_2)(2 - p(C_1)) = \frac{2}{R} \quad (18)$$

maximizes expression (16).

Eqns (17) and (18) define the so-called 'best reply' functions of, respectively, firm 1 and 2, and their solutions the Nash Equilibrium of the model [13]. This is the most widespread concept used in economics to predict in situations of strategic interaction, that is when an actor's best choice depends also on the choice of the competitors. Indeed, the solution C_1 of Eqn (17) depends on C_2 as well as the solution C_2 of (18) depends on C_1. Note that both Eqns (17) and (18) suggest that the larger is the R&D investment of the opponent, the lower the own R&D effort of a firm, and vice versa.

Given R, for each firm Eqns (17) and (18) provide a lower level of R&D investment than Eqn (3). In what follows I briefly investigate how much lower, in particular if and how the total R&D investment effort in the market changes with two firms.

Below I only take a first step, without aiming at generality, considering again the exponential success probability $p(C) = 1 - e^{-aC}$. It is immediate to check that in this case equations (17) and (18) are solved by $C_1 = C_2$. Therefore, it is important to discuss whether $C_1 + C_2$ is larger than $C_{EP} = \log(aR)/a$, the R&D investment level in the market with only one firm. To see this I differentiate Eqn (15) to obtain

$$\frac{dE\Pi_1(C_1,C_2)}{dC_1} = p'(C_1)R\left(1 - \frac{p(C_2)}{2}\right) - 1 \quad (19)$$

Evaluating Eqn (19) when the probabilities are exponential, and at $C_1 = \log(aR)/2a = C_2$, I derive that

$$\frac{dE\Pi_1(C_1,C_2)}{dC_1} = \frac{\sqrt{aR} - 1}{2} > 0 \quad (20)$$

and a similar conclusion would hold for $i = 2$. Decreasing returns from R&D imply that both expected profits $E\Pi_i(C_1, C_2)$ have negative second derivative and, because of Eqn (20), it follows that $C_1 = C = C_2$ solving Eqn (17), Eqn (18) is greater than $\log(aR)/2a$. Thus $C_1 + C_2 = 2C > \log(aR)/a$ that is the market R&D investments, in this case, are larger with two firms rather than with one firm. As a consequence, also the probability that at least one firm succeeds $1 - (1 - p(C))^2 = 1 - e^{-a2C}$ is larger than the success probability when only one firm is in the market $1 - e^{-a(\log(aR)/a)} = 1 - (1/aR)$. Therefore, with profit maximization competition would have a positive role in enhancing overall R&D effort and this might also suggest that competition can be beneficial to neglected diseases.

Concluding remarks

I think that the analysis conducted delivers some interesting insights. In case of one compound, a first important message is that when companies maximize ERR then while the decision on whether

or not to invest depends on both the success probability and the economic parameters, how much to invest depends only upon the success probability. In particular, for an ERR maximizing company a necessary condition to invest in R&D is that the success probability function should not exhibit decreasing returns for all *C*.

A second message, most important for this article, is that EP maximization will never induce lower R&D investments than ERR maximization. Therefore, if companies pursue ERR maximization we should expect them to invest in R&D no more than when they pursue EP maximization, possibly less.

Indeed, based on the argument in the section titled 'Economies of scope: a portfolio of compounds', the following result summarizes the generality of my conclusion.

Conclusion 2: For any form of the success probability, and any number of compounds in the portfolio, EP maximization will induce R&D investment levels that are never lower than those induced by ERR maximization.

This suggests that when pharmaceutical companies focus on productivity we should expect lower R&D investments for developing drugs treating neglected diseases.

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