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WHY REJUVENATION ATTEMPTS OFTEN LEAD TO CANCER AND WHY CYCLIC REJUVENATION IS BETTER: A SIMPLE QUALITATIVE EXPLANATION

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Abstract. Since the 1960s, biologists have shown that, contrary to the previous belief that ageing is irreversible, many undesirable biological effects of ageing can be reversed. First attempts to perform this reversal on living creatures were not fully successful: while mice achieved some rejuvenation, many of these rejuvenated mice developed cancer. Later experiments showed that these cancers can be avoided if we apply cyclic rejuvenation: a short period of rejuvenation followed by a longer pause. This modified strategy led to recent successes of mice that recovered their age-deteriorated vision and mice that recovered their heart tissue after a heart attack. However, why rejuvenation attempts often lead to cancer and why cyclic rejuvenation is better remained largely a mystery. In this paper, we provide a simple qualitative explanation of these two phenomena.

Keywords: rejuvenation, biological time reversal, cancer, cyclic application of rejuvenation.

1. Formulation of the Problem

Biological rejuvenation is possible. Until reasonably recently, biologists believed that ageing is an irreversible process: we may be able to slow it down by healthy lifestyle, but deterioration is inevitable and cannot be reversed. However, a deep analysis of the corresponding biological processed enabled researchers to show that biological rejuvenation *is* possible [2, 10]. For this ground-breaking research, John B. Gurdon and Shinya Yamanaka – the main authors of this discovery – received the 2012 Nobel Prize in Physiology or Medicine.

At first, the possibility of rejuvenation was shown on the cell level, but eventually, researchers showed that it is possible to rejuvenate the whole animal (specifically, a mouse) [3, 4, 6, 9].

Problem: rejuvenation often led to cancer. At first, researchers had great hopes that this technique can eventually be helpful for humans as well. However, further studies revealed an unfortunate (and often deadly) side effect: while the

rejuvenated aged mice indeed exhibited vital characteristics typical for younger animals, this rejuvenation led to a high occurrence of cancer; see, e.g., [1, 8].

Transition to a cyclic process helps. Further studies showed that cancer occurrences can be drastically decreased if instead of a previously used continuous rejuvenation process – when the corresponding chemical are applied for a certain time period – we use a cyclic process, when a short period of forced rejuvenation is followed by a longer period of no interference: e.g., 2 days of forced rejuvenation followed by 5 days of no interference; see, e.g., [7].

This approach has led to such successes as restoring vision in mice that became blind with age [**?**], and to regenerate mouse's heart tissue after the heart attack [11, 12].

But why? But why does rejuvenation often lead to cancer? And why does a cyclic application of rejuvenation work better?

In this paper, we provide a simple qualitative explanation for these facts.

2. Why Does Rejuvenation Often Lead to Cancer?

Rejuvenation means, in a nutshell, reserving direction of (biological) time. Rejuvenation means that we reverse the direction of the biological processes corresponding to ageing.

This time reversal is not limited to ageing. It is important to take into account that all the biological processes inside a body are highly related. Thus, when we reverse the biological processes corresponding to ageing, this affects other biological processes, so they may also get reversed – although probably not at the same level as processes corresponding ageing.

What other biological processes are affected by this time reversal? What are these other processes? Ageing is a visible process, in which the vital characteristics decrease with time. The reversal of these processes means that the values of these characteristics starts increasing, thus negative the effect of the previous ageing-related decrease. There are many other biological processes in which some characteristics decrease – processes which may be not so visible at first glance, but which are crucial for the survival of a living creature. Specifically, if there is any undesirable deviation from the optimal value of some characteristic, the body tries to bring the corresponding characteristic back to normal. For example:

- If the concentration of undesired bacteria becomes too large, the body tries its best to fight back and to decrease this concentration to a tolerable level.
- If the number of cells with undesired mutations increases beyond some threshold, the body starts actively attempting to destroy these cells, to bring their number to the tolerable level.

What does time reversal mean for these processes? For fighting against bacteria, time reversal means that, instead of decreasing, the concentration of

undesired bacteria will increase – i.e., that a small infection will cause a serious illness. While this is theoretically possible, in the laboratory conditions, when the mice experiments are performed, researchers try to preserve the purity of an experiment – and thus, the lab environment is regularly sterilized, to avoid any outside infections. So, in the corresponding experiments, there will probably be practically no undesired bacteria, so no serious illnesses will be observed.

On the other hand, mutated cells are always present. For these cells, time-reversal means that the number of such cells will start increasing – and this is exactly what is usually called cancer, when we have a rapidly increasing number of mutant cells. So, from this viewpoint, the appearance of cancer is very natural.

3. Why Does a Cyclic Application of Rejuvenation Work Better?

General explanation. Ageing-related rejuvenation happens very fast – in a few weeks, the results of several years of ageing are reversed. This rejuvenation is very fast because this is exactly the intent of this procedure: all the parameters of the rejuvenation procedure are selected so as to reach the maximal rejuvenation affect in a given moment of time.

As we have mentioned, because all biological processes are related, time-reversal of the ageing process is inevitably accompanied by time-reversal of other biological processes – in particular, processes that normally prevent most tumors to occur and that, when time-reversed, lead to cancerous tumor growth. However, this secondary effect is – as usual for secondary effects – much smaller than the original time-reversal effect for ageing. Thus, the reversal of this secondary process during a week does not reverse the changes that happened during years – as in the case of ageing – it only reverses the changes that happened probably during a few weeks.

So, if we perform the rejuvenation procedure for a short time (e.g., for a week) and then pause for a slightly longer time (e.g., for two weeks), the ageing effect of the rejuvenation will not be canceled – that would require a year-long pause – while the negative time-reversal side effect of this procedure will be eliminated by the pause. At a result, while the number of undesired mutant cells somewhat increases during the rejuvenation procedure, this increase is small and it is canceled by the later period and never reaches a dangerous level.

So, during each rejuvenation-pause cycle, we get an anti-ageing effect but the number of undesired mutant cells does not increase. So, if we repeat this cycle several times, we get a larger and larger anti-ageing effect, while avoiding the undesired appearance of cancer. This explains why a cyclic application of rejuvenation works better.

Illustration. Let us illustrate the above ideas in quantitative terms. Let us assume that each day, natural ageing decreases the value of a desired characteristic by a factor of $a < 1$ and that each day of rejuvenation procedure eliminates the effect of $N \gg 1$ days of ageing – i.e., increases the value of this characteristic by the value

a^{-N}. This way, if we apply this procedure for d days, we increase the value of the desired characteristic by $\left(a^{-N}\right)^d = a^{-N\cdot d}$.

What about the side effect? Let us denote the factor by which the number of mutant cells decreases during a week by m. For this process, time-reversal is not as efficient as time-reversal of ageing, so a day of anti-ageing rejuvenation procedure only cancels the effect of $n \ll N$ days of anti-mutant-cells fight. In other words, one day of rejuvenation increases the number of mutant cells by m^{-n}. If we simply apply this procedure for d days, we increase the number of mutant cells by a factor of $(m^{-n})^d = m^{-n\cdot d}$, which may be a significant (and even deadly) increase.

To avoid this side effect, let us follow each day of rejuvenation by a pause lasting, e.g., $n+1$ days. In this case, in each cycle, the desired characteristics first increases by a factor a^{-N}, and then decreases by a factor a^{n+1}. So, at the end of the cycle, we get an overall increase by a factor $a^{-N}\cdot a^{n+1} = a^{N-(n+1)}$. Since $n \ll N$, this is almost the same increase as in the situation when we do not make a pause, and just apply one day of rejuvenation. So, after d cycles, we gain practically the same rejuvenation effect as after d days of continuous rejuvenation. In other words, in terms of ageing reversal, the addition of pauses does not change the effect.

However, with respect to the side effect, the addition of pauses makes a drastic difference. Indeed, in this case, the initial increase by a factor of m^{-n} is followed by a pause-caused decrease by a factor of m^{n+1}. So, at the end of the cycle, the number of mutant cells changes by a factor of $m^{-n}\cdot m^{n+1} = m$. Since $m < 1$, this concentration decreases at the end of a cycle. So, after d cycles, the concentration of mutant cells decreases by a factor of $m^d \ll 1$.

The largest increase in concentration during these cycle is to the value m^{-n}, which is much smaller than the original increase to the level $(m^{-n})^d \gg m^{-n}$. If it so happens that this value m^{-n} is still too high – we can instead of performing rejuvenation of the whole day perform it for a few hours or even minutes – the anti-ageing effect will be largely the same, but the largest number of the mutant cells will be as close to the original one as we want. So, by choosing a sufficiently small rejuvenation period within each cycle, we can make sure that the number of mutant cells will never reach the danger threshold and thus, that cancerous side effects will be avoided.

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ПОЧЕМУ ПОПЫТКИ ОМОЛОЖЕНИЯ ЧАСТО ПРИВОДЯТ К РАКУ И ПОЧЕМУ ЦИКЛИЧЕСКОЕ ОМОЛОЖЕНИЕ ЛУЧШЕ: ПРОСТОЕ КАЧЕСТВЕННОЕ ОБЪЯСНЕНИЕ

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Аннотация. Начиная с 1960-х годов биологи показали, что, вопреки ранее существовавшему убеждению, что старение необратимо, многие нежелательные биологические эффекты старения можно обратить вспять. Первые попытки осуществить это обращение на живых существах не увенчались успехом: хотя мыши достигли некоторого омоложения, у многих из этих омоложенных мышей развился рак. Более поздние эксперименты показали, что этих видов рака можно избежать, если применять циклическое омоложение: за коротким периодом омоложения следует более длительная пауза. Эта модифицированная стратегия привела к недавним успехам мышей, у которых восстановилось ухудшенное с возрастом зрение, и мышей, у которых восстановилась ткань сердца после сердечного приступа. Однако, почему попытки омоложения часто приводят к раку и почему циклическое омоложение лучше, оставалось во многом загадкой. В этой статье мы даём простое качественное объяснение этих двух явлений.

Ключевые слова: омоложение, обращение биологического времени, рак, циклическое применение омоложения.

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