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The Game of the Pentose Phosphate Cycle

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Sugar rearrangement in the pentose phosphate cycle for transformation of six pentoses into five hexoses is analysed by abstraction to a mathematical model consisting of the resolution of a logical mathematical game of optimization. In the model, the problem is to arrive at five boxes containing six balls each, having started with six boxes containing five balls each, where boxes simulate the sugars and balls simulate the carbons in each. This is achieved by means of transferrring two or three balls from any box to any other in each step, according to transketolase and transaldolase (or aldolase) mechanisms which account for sugar interconversions in the living cell. A hypothesis of simplicity is imposed in order to arrive at the objective with the least number of steps and with the least number of balls in the intermediary boxes. A symmetrical solution is obtained, demonstrating that this is the simplest solution, which is the procedure carried out by biological systems. The same treatment is applied for sugar rearrangement in the non-oxidative phase of the Calvin cycle in photosynthesis and the analysis of the "L-type" of pentose phosphate cycle is also treated, obtaining similar solutions in both cases, which allow us to make some physiological reflections.

1. Introduction

The pentose phosphate cycle is an important metabolic pathway which occurs in many living cells, ubiquitously distributed among biological systems from bacteria to mammals (Axelrod, 1967; Tsolas & Horecker, 1972). Its biological function is extensive as an alternate pathway for glucose catabolism, as well as the main cytoplasmic source of NADPH, necessary

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for fatty acid synthesis and other reactions; this is also the source of erythrose 4-phosphate in the aromatic compound synthesis and the source of sugars of nucleic acids (Metzler, 1977; Pontremoli & Grazi, 1969). From the point of view of the nature of molecular transformation two phases can be considered: a first stage (oxidative phase), from glucose or glucose 6-phosphate to ribulose 5-phosphate, involving oxidations by $NADP^+$, decarboxylation and the opening of the ring, and a second stage (non-oxidative phase), from ribulose 5-phosphate to glucose 6-phosphate again, where only reactions involving sugar interconversions occur.

Let us consider the second stage described above, which accounts for sugar rearrangement. Metabolic mechanisms, according to catalytic properties of enzymes, only make possible sugar interconversions by means of reversible set transference of two or three carbons (C_2 or C_3) from any keto-sugar to any aldo-sugar with the condition that the keto-sugar must have S configuration in its third carbon. In fact, this second stage is the whole conversion of six pentoses (C_5) into five hexoses (C_6), all being phosphorylated derivatives and all intermediary products being phosphorylated surgars.

For this operative problem of converting six C_5 into five C_6, a mathematical solution can be obtained under conditions imposed by metabolic mechanisms, i.e. (1) only sets of C_2 or C_3 can be transferred from any sugar to any other by transketolase and transaldolase (or, eventually, C_3 can be drawn out of a keto-sugar by fructose 1,6-biphosphate aldolase), respectively, according to the catalytic properties of these enzymes (Shreve *et al.*, 1983; Tsolas & Horecker, 1973). In fact, although in each of these reactions the two substrates must be keto- and aldo-sugars, respectively, and the keto-sugar must have its third carbon in S configuration, there are isomerases and epimerases which account for interconversions of sugars with the same number of carbons. (2) It is not possible to have metabolic intermediaries with fewer than three carbons, since all stable intermediaries are sugars and any sugar must have at least three carbons.

Cellular conditions are only the two described above, but we can impose an additional condition of economy or simplicity: the total conversion of six C_5 into five C_6 must be made in the minimum number of steps and, furthermore, involving the least number of sugars with more than six carbons.

Considering only metabolic conditions, according to the mechanisms of reactions catalysed by transketolase and transaldolase (or aldolase) there are many solutions involving formation of C_8, C_9 and C_{10} intermediary sugars, which can have a variable number of steps. However, if the condition of simplicity is imposed, we are left with the metabolic pathway of the cell.

Our aim is to demonstrate that the cell solution is the simplest operative solution for this problem.

2. The Game

Abstraction of biological model to mathematical model is made by means of resolution of a logical mathematical game of optimisation, considering six boxes with five balls (six (C_5) each; thus, the problem is to obtain five boxes with six balls (five C_6) each, leaving one box empty, with the following conditions:

(1) *Hypothesis of the mechanism.* (a) Only two or three balls can be transferred in each step from one box to another. This operation is defined as one step. (b) When any box contains a certain number of balls, these cannot be fewer than three. These two conditions must always be observed in order to arrive at any solution.

In the pentose phosphate cycle, as occurs in cells, the two or the three carbons which are transferred are always the first of the keto-sugar (C-1 and C-2 for the set of two carbons transferred by transketolase, see Racker, 1961, or C-1, C-2 and C-3 for the set of the three carbons transferred by transaldolase, see Tsolas & Horecker, 1972), but this circumstance does not influence our mathematical hypothesis, since we can consider that the two or the three transferred balls in the game are precisely the first carbons of the sugar. The same assumption can be made with the sugars, since, although for cellular mechanisms one must be an aldose and the other must be a ketose with its third carbon in S configuration, epymerases and isomerases, not considered here, account for this reorganization. Therefore, in our game, the order in which elements of the problem are altered is not determinant in its solution and, thus, all the intermediary stages which have the same composition, although with a different order of elements, are equivalent.

(2) *Hypothesis of the simplicity.* Optimal solution must involve: (a) The smallest number of steps, where one step is the transfer of two or three balls from one box to another. (b) The smallest number of balls in the intermediary boxes during the solution process. There is no hierarchy in these two conditions; however, it is amazing that in this problem this hierarchy is not necessary because there is no alternative, since, as will be seen, the simplest solution is that which utilizes the smallest number of steps as well as the smallest number of balls in the intermediary boxes. In fact, it is not possible to find a solution which brings us closer to the first condition while moving away from the second, and the same occurs for the contrary case. It is possible to demonstate that the smallest number of steps is seven, with two intermediary boxes containing seven balls each, and that

a solution involving fewer than seven balls in two intermediary boxes is not possible.

The search for a solution is, therefore, reduced to a mathematical problem of minimisation, which can be restricted to getting from (555555) to (663366) which we can call "presolution", because the next step, from (663366) to (660666) is trivial. Since there is even number of boxes and even number of balls uniformly distributed, the problem can have a symmetrical solution, reducing it to transforming (555) into (663) for each half of the whole system, arriving thus at the "presolution" (663366); if this solution exists, it is simpler than any other non-symmetrical solution. Thus, our aim now is reduced to:

(a) Minimising the number of steps in three boxes to get the composition (663) from (555) with the condition of not obtaining any intermediary box with a number of balls greater than seven. In fact, a solution which does not contain at least one box with seven balls is not possible. *Demonstration*: In the set of stages to obtain any solution of the problem, according to the imposed conditions, there exists at least one box with seven balls, since the first step is obligatory and is (555) $\rightarrow$ (375) (or any other equivalent such as (537), etc.) because the other possible step, (285), or any other equivalent (such as (582)) does not take into account the imposed conditions, since it leaves a box with two balls.

(b) Realising the same process obtained in (a) for the boxes in the other half of the system, i.e. to obtain the composition (366).

We are allowed to operate independently with (a) and (b), since in each step only two boxes can and must participate—the donor and the receiver.

3. The Solution

Now we have three boxes with five balls apiece and we want to arrive at two boxes with six balls and one with three balls, i.e. from (555) to (663). It could be that there is no solution for this, but if it exists, the simplest solution for it is also the simplest solution for the total problem.

The first step is necessarily (555) to (375)—as is demonstrated above. Now we must arrive at (663) from (375). The immediate step for the appearance of the first 6, according to the imposed conditions is for 7 to disappear and for 6 to appear, i.e. (375) to (645). In fact, according to the imposed conditions, from (375) the following results can be obtained in one step: (a) (555); (b) (357); (c) (645); (d) (348); (e) (573) and (f) (393). Option (a) lead us to the preceding situation and options (b) and (e) do not involve any progress on our way to the solution, giving more complicated procedures for the same result, all of which must be discarded according to the hypothesis of simplicity. Options (d) and (f) lead us to more complicated stages, involving boxes with more than seven balls and they must also be discarded for the same reason. Thus, in all cases, conditions of simplicity oblige us to take option (c), i.e. from (375) to (645). Now it remains for us to arrive at (663) from (645) which can be done in only one step. The solution is, therefore, for the half of the symmetrical whole: (555) → (375) → (645) → (663) in three steps, any other solution being more expensive. It is thus demonstrated that the three steps to convert (555) into (663) are irreducible, this being the simplest solution.

4. Conclusion

According to the symmetrical division of the problem and the described solution, three steps are necessary to transform (555) into (663) in each

TABLE 1

Complete procedure for arriving at five boxes containing six balls each, having started with six boxes containing five balls each. Symmetrical division of the problem is a possible method of finding a solution. The simplest solution described in this Table has seven steps, with two intermediary boxes containing seven balls each. This procedure is the same as occurs in the non-oxidative phase of the pentose phosphate cycle in biological systems (see Fig. 1) where steps 1 (A or B) and 3 (A or B) are catalysed by transketolase, steps 2 (A or B) are catalysed by transaldolase, and step 4 is catalysed by fructose 1,6-biphosphate aldolase

	(5	5	5)	(5	5	5)	
1A							
	(3	7	5)	(5	5	5)	
2A							
	(6	4	5)	(5	5	5)	
3A							
	(6	6	3)	(5	5	5)	
							1B
	(6	6	3)	(5	7	3)	
							2B
	(6	6	3)	(5	4	6)	
							3B
	(6	6	3)	(3	6	6)	
4							4
	(6	6	0	6	6	6)	

symmetrical half of the whole system, giving a total number of six step: seventh step is now necessary to obtain (660666) from the obtained pre: ution (663366). Thus, it is demonstrated that under imposed conditic the solution reaches its optimisation in the seven described steps and in case does the number of balls in each box surpass seven. Since in procedure all solutions involving more than seven balls in any intermedi box have been discarded and, as demonstrated above, it is not possibl find a symmetrical solution with fewer than two boxes with seven ball: is demonstrated that it is not possible to find a solution simpler than one developed here without disturbing the hypothesis of the mechani It is concluded, therefore, that it is necessary to accept *a fortiori* the th developed herein. Table 1 expresses the total procedure. It can be seen t this solution is the same as that occuring in biological systems (Fig. 1)

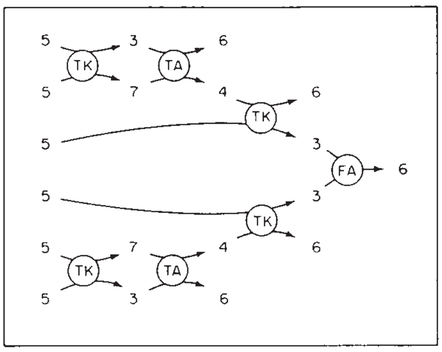

FIG. 1. Non-oxidative phase of the pentose phosphate cycle, as occurs in biological syst for the rearrangement of six pentoses into five hexoses. Reactions catalysed by isomer and epimerases are not represented, the figure showing only reactions involving transformat of the number of carbons among surgars. FA, fructose 1,6-biphosphate aldolase; TA, tra dolase; TK, transketolase. Numbers express the numbers of carbons in every sugar.

must be kept in mind, however, that the solution described in Table 1 d not imply a hierarchical order in the operations of the two sets of tl boxes. It is therefore possible to operate independently with each on order to arrive at the "presolution" (663366). The only necessary condit is that in each case, each of the three steps 1A, 2A, 3A and 1B, 2B, 3E correlative. That is, step 2A must be effectuated after 1A and before the same occurrring for set B, but the operations of the two sets independent. This means that the solution expressed in Table 1 may achieved in many ways, as is represented in Fig. 2.

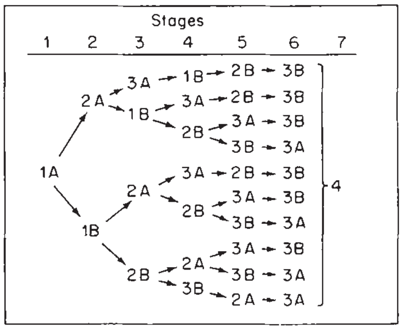

FIG. 2. Different possibilities for operating with the steps of the solution in the two symmetrical sets of three boxes. The seven steps necessary to convert six pentoses into five hexoses can be arranged in any way indicated in the figure. All these ways are equivalent since they involve exactly the same steps, although differently ordered in each set of three boxes (e.g., step 2A is always after 1A; 3B is always after 2B etc. Only the independence among steps A and B is represented in this scheme). These are, thus, different forms of to put into practice the same solution. A similar scheme can be made for photosynthesis and "F-type" of the pentose phosphate cycle.

5. The Calvin Cycle in Photosynthesis

The same reasoning can be employed to resolve the problem of sugar rearrangement in the non oxidative stage of dark phase in photosynthesis. Now the problem is to transform 12 sugars of three carbons (gyceraldehyde 3-phosphate or dihydroxyacetone phosphate) into six sugars of five carbons (ribulose 5-phosphate) and one sugar of six carbons (fructose 1,6-biphosphate) by using enzymes similar to those in the pentose phosphate cycle, i.e. enzymes which transfer two carbons (transketolase) and enzymes which transfer three carbons (transaldolase and aldolases). A similar logical mathematical game can be designed with the same hypothesis as in the preceding case, involving the same conditions of mechanism and simplicity, to arrive at six boxes containing five balls each and one box with six balls, leaving five empty boxes, from 12 boxes containing three balls each. The simplest solution is demonstrated by the same procedure described above, also by a symmetrical division as in the preceding case. Thus, the simplest solution (Table 2) involves nine steps with only two intermediary boxes containing seven balls, the same procedure as that occurring in biological systems (Fig. 3). Observe that in this case use is not made of transaldolase; if this enzyme were obligatorilly used, it could imply a more complex solution with a greater number of steps or with boxes containing more than seven balls.

TABLE 2

Complete procedure for arriving at six boxes containing five balls each, and one box containing six balls, having started with 12 boxes containing three balls each. Symmetrical division of the problem is possible to find a solution. The simplest solution described in this Table has nine steps with two intermediary boxes containing seven balls each. This procedure is the same as occurs in the non-oxidative phase of the Calvin cycle in photosynthesis (see Fig. 3) where steps 1 (A or B), 3 (A or B) and 9 are catalysed by aldolases, and steps 2 (A or B) and 4 (A or B) are catalysed by transketolase

	(3	3	3	3	3	3)	(3	3	3	3	3	3)	
1A													
	(0	6	3	3	3	3)	(3	3	3	3	3	3)	
2A													
	(0	4	5	3	3	3)	(3	3	3	3	3	3)	
3A													
	(0	7	5	0	3	3)	(3	3	3	3	3	3)	
4A													
	(0	5	5	0	5	3)	(3	3	3	3	3	3)	
													1B
	(0	5	5	0	5	3)	(3	3	3	3	6	0)	
													2B
	(0	5	5	0	5	3)	(3	3	3	5	4	0)	
													3B
	(0	5	5	0	5	3)	(3	3	0	5	7	0)	
													4B
	(0	5	5	0	5	3)	(3	5	0	5	5	0)	
9													9
	(0	5	5	0	5	0	6	5	0	5	5	0)	

6. The "L-type" of the Pentose Phosphate Cycle

Williams *et al.* (1978*b*) have proposed a rather different and more complex pathway for the pentose phosphate cycle in liver, named "L-type" which includes intermediaries of eight carbons (octulose 8-phosphate and octulose 1,8-biphosphate) besides arabinose 5-phosphate and sedoheptulose 1,7-biphosphate; in this pathway, transaldolase is not included as functional enzyme and aldolase participates in three ways, giving or splitting fructose 1,6-biphosphate, sedoheptulose 1,7-biphosphate and D-glycero D-ido octulose 1,8-biphosphate. The classical pentose phosphate cycle discussed above (see Fig. 1) has been named "F-type" by these authors, as a typical pathway of fat tissue (see Williams, 1980). A controversy over the sequence and mechanism of the pentose phosphate cycle has been widely

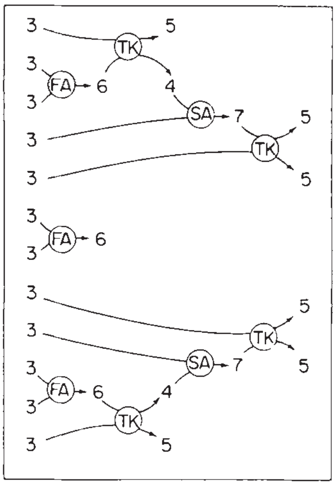

FIG. 3. Non-oxidative phase of the Calvin cycle in the dark phase of photosynthesis, as occurs in biological systems for the rearrangement of twelve trioses into six pentoses and one hexose. Reactions catalysed by isomerases, epimerases and phosphatases are not represented, the figure showing only reactions involving transformations of the number of carbons among sugars. FA, fructose 1,6-biphosphate aldolase; SA, sedoheptulose 1,7-biphosphate aldolase; TK, transketolase. Numbers express the number of carbons in every sugar.

discussed (see Katz, 1981; Landau, 1981; Wood, 1981; Williams, 1981; Landau & Wood 1983).

It is not the purpose of this work to participate in this controversy, but we consider that the metabolic pathway proposed by Williams and co-workers can also be treated here, in light of the same procedure as that described above, by using a similar mathematical model. The problem is the same: starting from six boxes with five balls each one, the objective is to obtain five boxes with six balls each, leaving one box empty, although some new conditions are now imposed. The hypothesis of simplicity remains the same as described above, but in the hypothesis of the mechanism a new condition is observed: because no transaldolase action is considered in the procedure, it is not possible to transfer three balls from any box to another, while leaving some balls in the two boxes which participate in the step. Thus, the hypothesis of the mechanism remains as follows: (a) Only two or three balls can be transferred in each step from one box to another. This operation is defined as one step. (b) For transferring two balls, there are no restrictions: this can be done in whatever situation as long as all other conditions of this hypothesis are respected. These operations represent steps catalysed by transketolase, where a set of two carbons is transferred from one sugar to another. (c) For transferring three balls it is necessary that an empty box participate in the operation, i.e. it is possible, for example, to make (633) → (660); (643) → (670); (870) → (573) etc., but an operation like e.g. (843) → (546) is not possible. It is possible, therefore, to transfer three balls from any box (with more than five balls, according to the (d) condition) to an empty box, or to transfer three balls from any box which contains only three balls to another box, the first box after the operation remaining empty. Thus, this operation represents the aldolase mechanism, leaving the transaldolase mechanism out of the possibilities, out of our game. (d) When any box contains a certain number of balls, these cannot be fewer than three. All these conditions must always be observed in order to arrive at any solution.

With these new conditions, the problem can be resolved by the same procedure. A symmetrical solution can be found and the transformation of (555) into (663) is given by the following steps.

(1) The first step is (555) → (375) as demonstrated previously, since the hypothesis of the mechanism for transference of two balls has not been altered and the other alterations have imposed more restrictive conditions. It is demonstrated, thus, that with these new conditions, a solution is not possible which contains at least one box with seven balls in each symmetrical half of the system, as in the "F-type" of the pentose phosphate cycle. Now, it can be demonstrated that in these new conditions, for "L-type", a solution which does not contain at least one box with eight balls is likewise not possible.

(2) The second step starts from (375). From this, by transference of two balls, we can arrive at (555), (357), (393) and (573), where only (393) is a progressive result, all other results must be excluded, according to the hypothesis of simplicity; and, by transference of three balls, we can arrive at (3345) or (780); the first is not possible since it needs four boxes, only having three. It is therefore necessary to choose between (393) and (780). In any case, a progressive result involves at least one box with more than seven balls, which demonstrates the proposition enunciated above. The hypothesis of simplicity leads us to choose (780), since it involves boxes with fewer balls, and to discard (393).

(3) From (780), by transferring two balls, we can obtain (960) or (5 10 0) and, by transferring three balls, we can obtain (753) or (438), the two first results are discarded according to the hypothesis of simplicity; (753) is also discarded for the same reason, since it leads us to a previous situation and we therefore choose (438) as necessarily the best.

(4) The following step is obviously the transfer of two balls from the box of eight balls to eliminate the eight thereby leaving six. It leads us to

the "presolution" and, as we can arrive at this in only one step, the choice has no alternative. The solution is, thus, (555) → (375) → (780) → (438) → (663) in four steps, any other solution being more expensive. In fact, if in the second step (393) is chosen instead of (780), the number of steps is not reduced at the expense of increasing the number of balls in the intermediary boxes, since the procedure must be continued to (690) and (663); i.e. (555) → (375) → (393) → (690) → (663). This solution also has four steps but it involves a box with nine balls, whereas the solution selected has no box with more than eight balls. This shows also that in the search for the simplest

TABLE 3

Complete procedure for arriving at five boxes containing six balls each, having started with six boxes containing five balls each, according to the hypothesis of the mechanism proposed for the "L-type" of the pentose phosphate cycle by Williams et al. (1978b). Symmetrical division of the problem is possible to find a solution. The simplest solution described in this Table has nine steps, with intermediary boxes containing seven and eight balls. This procedure is the same as described by Williams and co-workers for the liver pentose phosphate cycle (see Fig. 4). Steps 1 (A or B) and 4 (A or B) are catalysed by transketolase and steps 2 (A or B), 3 (A or B) and 9 are catalysed by aldolase

	(5	5	5)	(5	5	5)	
1A							
	(3	7	5)	(5	5	5)	
2A							
	(7	8	0)	(5	5	5)	
3A							
	(4	3	8)	(5	5	5)	
4A							
	(6	6	3)	(5	5	5)	
							1B
	(6	6	3)	(5	7	3)	
							2B
	(6	6	3)	(0	8	7)	
							3B
	(6	6	3)	(8	3	4)	
							4B
	(6	6	3)	(3	6	6)	
9							9
	(6	6	0	6	6	6)	

solution the algorithm we have used can be applied: in each step, we must choose the progressive result with fewer balls in its fullest box. Table 3 expresses the total procedure, the same as that proposed by Williams *et al.* (1978*b*) for the "L-cycle" (Fig. 4).

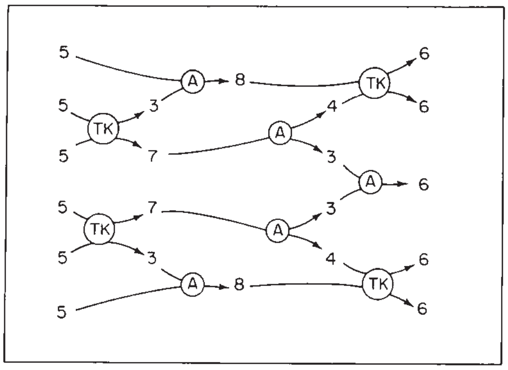

FIG. 4. Non oxidative phase of the "L-type" of the pentose phosphate cycle as described by Williams *et al.* (1978*b*), for the rearrangement of six pentoses into five hexoses in liver. Reactions catalysed by isomerases, epimerases and phosphotransferases are not represented, the figure showing only reactions involving transformations of the number of carbons among sugars. A, aldolase; TK, transaldolase. Numbers express the number of carbons in every sugar.

7. Discussion

The analysis of the pentose phosphate cycle and related metabolic pathways by means of the mathematical model here described suggests some comments about the logic of living systems and the concordance among biological mechanisms of the catalysed reactions and the optimization in mathematical models.

First, it appears that biological evolution has pursued a logical line in sequences of reactions so that the passage between precursor and product is achieved with the minimal number of steps. It is applicable to the classical pentose phosphate cycle ("F-type"), as well as the non-oxidative phase of the Calvin cycle in photosynthesis. With respect to the "L-type" of the pentose phosphate cycle, as proposed by Williams and co-workers, it is also applicable, but we think it is pertinent to make an observation. The "L-type" involves different enzymes and, thus, in the model, they are represented by different hypotheses of the mechanisms. It can only be concluded that with such different hypotheses, the simplest solution of the model is in agreement with the "L-cycle" proposed by these authors. It is not possible, with this treatment, to resolve the controversy between "L" and "F" types since all of them are consistent with the solution of each problem, bearing in mind each particular hypotheses of their mechanisms (i.e. transaldolase acts only in "F-type"). The question, then, is the explanation for the occurrence of "L-type" which involves the discarding of the transaldolase mechanism, the liver having an activity of this enzyme greater than that of transketolase in rat and rabbit (Williams *et al.*, 1978*a*). The question is, thus: why does transaldolase not act in liver? because under its activity there is a simpler solution ("F-type"). In the Calvin cycle, however, the situation is very different. As can be seen in the solution (Fig. 3 and Table 2), transaldolase does not appear in the optimal procedure, and indeed as the solution of the game coincides with the biological pathway transaldolase is not necessary.

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