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Hypothesis

On the origin of the genetic code

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Abstract A series of stages in the evolution of the genetic code is postulated, representing a chain of logical steps that leads to the present-day code. The stages described are based on translation machinery between the RNA world and that of amino acids, a model that consists of an RNA assembler strand along which RNA hairpin molecules are lined up, forming a picket-fence-like aggregate. Each hairpin carries an amino acid at the bottom of one of its legs, and the mutual proximity of amino acids achieved in this way facilitates their linkage into oligopeptides, in a sequence governed by the nucleotide sequence along the assembler strand, the code. The order in which amino acids are introduced into the code is in the approximate order of their availability, tempered by polarity and structural considerations.

Key words: RNA hairpin; tRNA precursor, mRNA precursor; Hairpin assembly; Genetic code; Evolution

1. Introduction

In this paper, we present model steps in the evolution of the genetic code, starting with a code for just two amino acids. Our approach involves the previously proposed model of a device [1–5] that serves to translate RNA-based codes into oligopeptides. This device is a picket-fence-like arrangement of RNA hairpins that, on the one hand, are linked by a triplet of nucleotides in their loops to complementary nucleotides along an open (i.e. unfolded) RNA strand and, on the other hand, carry amino acids at their other ends (Fig. 1).

The closeness of amino acids thereby attained greatly speeds their linkage into oligopeptides, the sequence of which is determined by the sequence of nucleotides, the carriers of the code, in the open RNA strand. We term the open strand the 'Assembler strand' (or A-strand) and the entire device the Hairpins-Assembler-strand device (HA-device). In our model the A-strand gradually evolves into mRNA, the hairpins into tRNAs, and the HA-device into the ribosome as it slowly is modified by rRNA and increasingly sophisticated proteins.

We first recapitulate the evolutionary events and gradients needed for the development of this model HA-device. This is followed by what we believe to be plausible steps in the evolution of the genetic code (Fig. 2). See references [6–16] for different approaches.

The procedure that characterizes our model is to ask even after the smallest steps, what evolutionary circumstances provide a gradient towards further evolution and how these gradients are utilized? Such a modelling of detailed steps, each of them feasible on chemical, physical, and probabilistic grounds, and rewarded by evolutionary benefits, is basically different from an approach that searches for selforganizing processes that lead to dissipative structures in homogeneous phases, as in a primeval ocean. It is very striking that a tightly confined path characterized by such questions inescapably appears to lead to a very specific genetic apparatus, genetic code and emergence of life-like forms.

At the present time the origin of life is unknown, but it is nevertheless possible to build a structural model of the early steps of life [17], a model that is based on current knowledge of molecular biology and prebiotic chemistry [18–24].

2. A short template strand marks the beginning

An important requirement is a solution of two kinds of monomers capable of assembling covalent links into short polymer strands. The two kinds of monomers must be 'complementary' in such a way that they weakly attract each other, e.g. by hydrogen-bonding, and may link as they line up on the template. Each new strand can then serve as template for further strands. Among candidates for these monomers are the nucleotides guanosine (G), cytidine (C), adenosine (A), and uridine (U). We favor G and C for the beginning, because they base-pair with three rather than two hydrogen bonds. The incident signalling the dawn of life is an unusual event that occurs, for instance, during drying and re-dissolving of a solution, and leads to the formation of the first short template strand.

Further essentials are temporal conditions consisting of a suitable program of cyclical temperature changes that drive strand replication, and spatial conditions providing compartmentation. These may be given by day-and-night and various shadow-casting cycles and pores in rocky material.

3. Evolution requires replication errors and graduated confinement

An essential ingredient is a rare error in replication. While most of these errors are 'detrimental', others are not, and if such an error imparts an advantage upon the replicate strand, improving its adaptation to environmental conditions, its descendants eventually replace their less efficient fellow strands. In other words, there needs to be variation and selection.

What is most important at this point is the presence of a neighbouring region, suffused by monomers, with pores that offer almost, but not quite adequate confinement for the exist-

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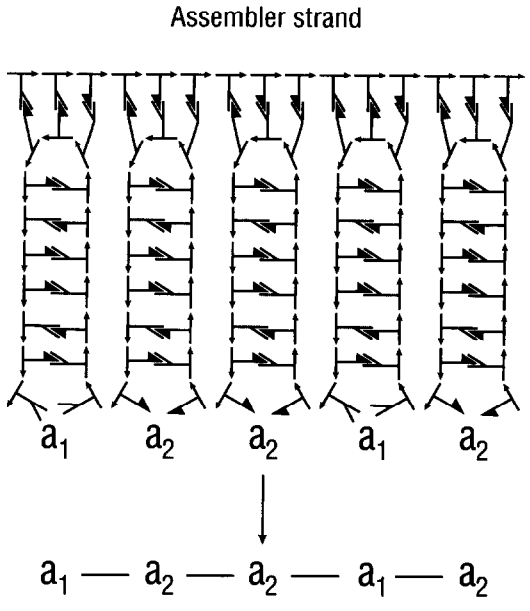

Fig. 1. Hairpins-assembler-strand (HA-) device. Lateral weak attraction of hairpins leads to the formation of a picket-fence-like aggregate. An assembler strand greatly assists its formation. Codons in RNA assembler strand (A-strand) base-pair to anticodons in loops of RNA hairpins that carry amino acids (bottom) and thereby catalyze the formation of oligopeptides. In stage A (Fig. 2) codon–anticodon pairs in middle of codons are related to amino acids tied to hairpins.

ing short strands. Such a region provides an evolutionary gradient for strand lengthening. Pores with yet larger openings can be colonized by yet longer strands or by other structures, large enough to be constrained from being lost by diffusion. Thus, while most copying errors are lethal or detrimental, rarely and by chance they will promote colonization of new diverging regions.

4. Hairpins and an error filter

The direct synthesis of large strands is more difficult since more monomers are involved, but this obstacle can be overcome by strand doubling during rare events, such as partial drying and re-dissolution in a suitable location. However, replication errors set an upper limit to this process as well. In the model, this limit is overcome by an error filter that eliminates most but not all flawed strands.

Some strand variations can fold back onto themselves and form weak bonds between complementary nucleotides, a conformation that is favored because of the protection against chemical attacks afforded by the proximity of monomers linked in this fashion. The most favorable conformation is a hairpin (Fig. 3a,b), and there will be convergence to it.

Two aspects of the hairpin conformation are of great importance. The first is that it requires an antiparallel monomer orientation, as is evident from Fig. 3. This also implies antiparallel strand replication and antiparallelity between A-strand and attached hairpin strands. The other aspect is that not only the replicate of a hairpin is again a hairpin, but these two hairpins (which we can arbitrarily label (+) and (−)) have also different nucleotides only in the middle of their loops (Fig. 4). This is important for the establihment of the very first, primitive translation device between nucleotides and amino acids.

More protection against outside attack and decomposition into monomers is provided by lateral attraction of these hairpins, furnished in our model by the intercalation of Ca^{2+} or Mg^{2+} ions, which leads to the formation of picket-fence-like hairpin aggregates. Evolutionary gradients favoring such a configuration also involve the increase in size over single hairpins, which makes colonization of larger pores possible and the extremely important fact that such an aggregation implements an error filter. That is, any imperfect hairpin copy that does not fit into the aggregate is rejected and falls prey to chemical attack or dispersion by diffusion. However, errors that do not affect incorporation into the aggregate are not lethal, and without such rare errors evolution would cease.

5. The assembler strand

An important improvement in our model is an open (i.e. unfolded) strand of monomers to which the monomers

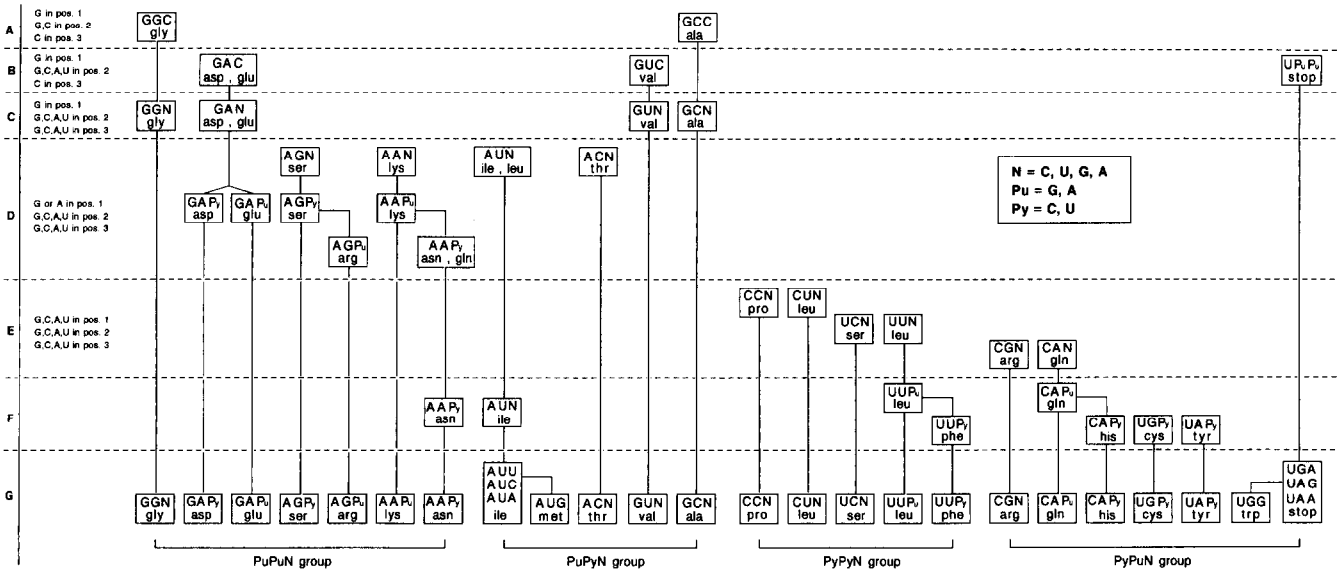

Fig. 2. Evolution of the genetic code. The different hypothesized stages are based on arguments concerning availability of amino acids (Table 1, notes (a)–(k)).

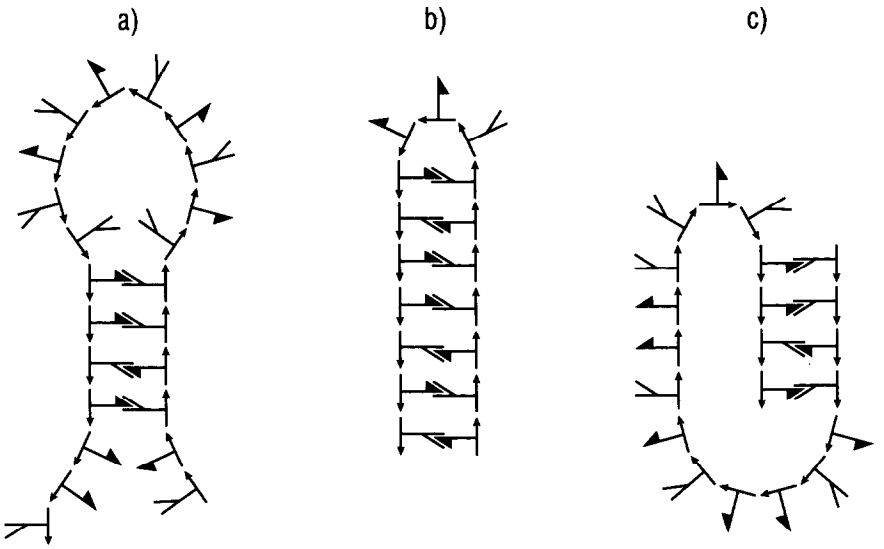

Fig. 3. Hairpin formation. (a) Incomplete hairpin conformation, with antiparallel attraction of monomers. (b) Complete hairpin conformation. Note that this conformation requires antiparallel attraction of monomers. (c) Parallel attraction of monomers does not allow hairpin conformation and therefore does not afford maximum protection against outside chemical attack.

in the loops of the hairpins can attach. Such a strand greatly speeds the formation of interlocking picket-fence-like aggregates of hairpins and thereby provides a strong selective advantage.

We imagine that an A-strand might work as a guide, leading a new hairpin to an HA-device during its building process when the hairpin is only loosely attached to the A-strand and therefore still mobile and capable of changing position along the A-strand. In this way, the A-strand would convert three-dimensional diffusion into one-dimensional diffusion. The presence of the A-strand is crucial to the firm fixation of a new hairpin into the aggregate. We assume that the final incorporation of hairpins into the HA-device requires complementary bonding between nucleotide triplets in the hairpin loops and nucleotide triplets in the A-strand.

Note that open strands always exist, because of errors in the replication of hairpins. They are usually lost by diffusion but if, by chance, one of them has the appropriate sequence for serving as A-strand, even for the binding of only two or three hairpin loops, it becomes part of the system; that is, many of its replicas would still diffuse away, but others would be kept by being part of HA-devices. Once in existence, such a strand-aided assemblage of hairpins is greatly favored by selection.

6. Oligopeptides assist the colonization of new regions by acting as agglutinants and improve replication by intercalation

The final step leading to the HA-device is the attachment of amino acids to the hairpin legs. In the HA-device, they are side by side, and their nearness greatly bolsters covalent bond formation between them (Fig. 1). Assuming that the very simple oligopeptides made in this fashion are capable of agglutination, they assist the restraining function of pores by narrowing pore openings, and making larger pores accessible to colonization, which provides an evolutionary gradient. The exact monomer sequence of oligopeptides is not important at this stage, as long as there is agglutination.

At a later time, other beneficial oligopeptides are formed. Their function might be to assist the reproduction of strands and hairpin aggregates, perhaps by some kind of intercalation during the copying process, making this process more accurate and faster. Of course, all such 'favorable' oligopeptides arise only rarely, by chance. Moreover, until there is a way in which advantageous sequences are 'remembered', they have only temporary value, because the very copying errors that led to their creation will also destroy them eventually. In due time, how-

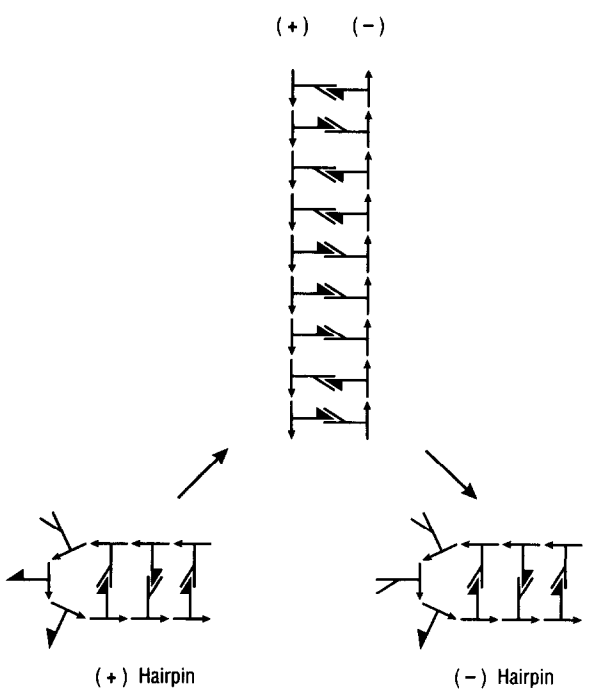

Fig. 4. Template-assisted strand replication, and assumption of a hairpin conformation by the two separated strands. Note that the two monomer sequences are identical, with the exception that the monomers in the center of the loop are complementary.

ever, beneficial oligopeptides will improve replication to the extent that a firm relationship develops between the nucleotide sequence of the A-strand and the amino acid sequence of the oligopeptides. This represents the rudiments of a code.

The kind of required evolutionary gradient is always the presence of a region that can almost but not quite be populated by any of the reproducing devices existing at the time. If there occurs one of the rare beneficial random errors in one of the copying stages, which enables the resulting daughter copy to colonize the region, it will do so. That is, the daughter strand must be capable of utilizing the opportunities available in the hitherto uncolonized region to survive and to multiply sufficiently to be selected.

It is also characteristic to our model that it is not tied to its specific terrestrial realization. Important aspects of the model – antiparallel template-driven replication, antiparallel attachment of hairpins to A-strands, reading frame and triplet attachment of hairpins to A-strands (see below) – do not depend on specific monomers although, of course, quite definite requirements must be met by suitable monomers.

7. Triplet attachment of hairpin loops to A-strand

In our model, the firm integration of each hairpin requires the linkage of three adjacent monomers in the hairpin loop to three complementary monomers along the A-strand, in addition to a weak lateral attraction between neighboring hairpins, which is caused by the intercalation of Mg^{2+} or Ca^{2+} ions. First steps in an experimental realization of this model support such lateral attraction between neighboring hairpins, as well as complementary bonding between triplet pairs of nucleotides in the hairpin loops and in the A-strand [25,26].

The nucleotides of an A-strand are thus arrayed into adjoining triplets, and to each triplet is attached a complementary triplet in the loop of a hairpin. The reason for this 'triplet' assumption is that it provides the smallest number of complementary nucleotides for a firm and stable aggregate.

We imagine that during the formation of an HA-device each new hairpin is first attracted laterally to the previously attached hairpin and by chance may slide up to the strand where complementarity between nucleotides in the first position is important for proper 'docking'. Base-pairing in positions 2 and 3 is also important to assure precision in the formation of error-free aggregates at first, but complementarity in position 3 is gradually relaxed in intermediate stages, to become important again as the requirements for survival demand the use of position 3 for a more elaborate code.

An attachment involving more than triplets is not optimal. The higher the number of complementary nucleotide pairs providing the attachment is, the more complex the accompanying logistics, the more wobbly and rickety the resulting picket-fence-like aggregate, and the less rapid its assembly are. Triplets offer also sufficient coding possibilities, and unless really required for coding needs, an attachment by more than three monomer pairs would represent an evolutionary burden rather than an advantage.

8. The earliest phase

At the beginning the nucleotides G and C were most important, as mentioned earlier, and the most prevalent amino acids were alanine and glycine. The earliest 'code' in our model involves just these two nucleotides and two amino acids. The fact that complementary hairpins differ only in the middle of their loops is of crucial importance for the earliest HA-device The earliest HA-device contained just the near-identical (+) and (−) versions of the 'same' hairpin differing at the very end of their legs (Fig. 1). They must be slightly different at their leg ends because (+) and (−) hairpins have to carry different amino acids; the complementarity requirement for monomers at the leg ends must therefore be relaxed. The stability of HA-devices, built from such near-identical hairpin neighbours is, of course, favorably affected by their close fit.

We make the assumption for reasons detailed below, that hairpins with C in the loop were invested with glycine, and 'G-hairpins' with alanine. Therefore, looking at the middle nucleotide of a triplet along an A-strand, G would 'code' for glycine, and C for alanine. There is, however, another requirement to be met, because there is a need for recognizing the location of different code letters on the A-strand, a need for a 'reading frame'.

9. The reading frame requirement

In the early stages of evolution, there is the demand for a way of telling where a triplet along the A-strand begins and ends, i.e. there has to be a reading frame. Specifically, our model requires that in all triplets along the A-strand, the first nucleotide must be G and the third must be C, assigning any coding function to the middle nucleotide. The reading frame has therefore the form 5′-GNC-3′, where N first stands for G or C and later for A or U as well. For a corresponding hairpin loop, the sequence complementary is 3′-CN′G-5′ or 5′-GN′C-3′, N′ being the nucleotide complementary to N. However, as the loops of complementary (+) and (−) hairpins differ in the middle nucleotide only, they are both of the same type, 3′-CN′G-5′. This implies that the same GNC reading frame applies to both, (+) and (−) hairpins.

At a later stage, when the evolving ribosome begins to stabilize the attachment of hairpins to the assembler strand, the reading frame gradually looses in importance. At that time triplet position 1 is also pressed into coding service, and finally all three positions are used for this.

10. The polarity argument

As the code evolves, the sequence of incorporation of the amino acids is mainly governed by their abundance, tempered to some degree by structural considerations (Table 1). Another important factor concerns the polarity of the amino acids [32]. We hypothesize that today's relationship of a purine base (Pu) in codon position 2 to a polar amino acid, and of a pyrimidine base (Py) to a nonpolar or weakly polar amino acid, has existed since the earliest stages. We use this as a criterion for resolving ambiguities in some assignments: we couple A with the more polar and G with the less polar amino acids, and for nonpolar and weakly polar acids, we assign the nonpolar one to U and the weakly polar one to C. Thus in the earliest stage of evolution we assume that G in position 2 associates with glycine and C with alanine. Hence, in our model the sequence 5′-GGC-3′ is the earliest codon for glycine, and 5′-GCC-3′ that for alanine, glycine being the more polar of the two.

11. Stage by stage evolution of the code

Each step of relaxation of constraints on the code by improvement of the translation machinery confers a selective advantage, increasing the number of amino acids that can be coded for. It is, however, important to recognize that the final, explosive emergence of 'life' and its divergence in many different directions becomes possible only through the presence of many cooperating HA-devices, each providing a beneficial oligopeptide. These functional units are integrated by enclosure in an envelope (for a detailed discussion see [17]).

As a brief overview, evolutionary stages that follow the earliest code (stage A, Fig. 2) are these: while in stage A position 2 is occupied by G or C, in later stages A or U also become acceptable, leading to the codons GNC in stage B, where N denotes G, C, A, or U. Next, the need for restrictions in position 3 is relaxed and this position can be occupied by G, C, A, or U (stage C (GNN)). Later, the nucleotide in position 1 need no longer be G, but still must be one of the two purine bases A or G, either of them denoted by Pu (stage D (PuNN)). And last, all base sequences are allowed (stages E,F,G (NNN)). The details are these:

Stage B, GNC

Depending on the environment, the use of A and U as code letters, in addition to G and C, can have selective advantages. The transition temperature from hairpin to open conformation which is needed in strand replication, strongly depends on the GC/AU ratio of the hairpin, and a certain ratio is optimal for given environmental conditions. Nevertheless, the importance of a GNC reading frame at this early stage demands that only in position 2 can G and C be supplemented by A and U. (Our GNC frame resembles Crick's PuNPy comma-free reading frame [9]; his model, however, does not involve the HA-device but is based on a flipping mechanism.)

The amino acids that follow glycine and alanine in abundance, are aspartic acid, glutamic acid and valine (Table 1). According to our polarity assumption, the codon GUC will be associated with the nonpolar Val and GAC with the polar Asp/Glu, the last two amino acids being interchangeable at this stage.

As more and more amino acids are incorporated, there is a need for stop codons. Such codons should differ as much as possible from GNC. Instead of the purine G in position 1, there should be a pyrimidine (C or U, the weakly binding U being better), and in position 3, there should be a purine (G or A). Position 2 should hold a purine because it is known that hairpins with Py in the loop bind less well to the complementary Pu in the assembler strand than vice versa [25]. This yields the stop codons UPuPu.

Stage C, codons GNN

The sequence GNC, used to maintain the reading frame, gradually loses importance, because of the increased efficiency of the translation device. However, only position 3 is thereby opened for all bases; positions 1 and 2 retain their importance for the proper incorporation of new hairpins.

Stage D, codons PuNN

The maintenance of the triplet reading frame no longer requires that location 1 be taken up by G, and the purine A can serve the same purpose. Hence the codons AUN, AGN, ACN, and AAN become available for the amino acids leucine/isoleucine, serine, threonine and lysine, next in sequence in Table 1. Using our polarity assumption we associate the codons AGN and AAN with Ser and Lys (moderately and strongly polar), and AUN and ACN with Leu/Ile and Thr (nonpolar and weakly polar).

Table 1
Sequence of amino acids in the order in which they were coded for. *Columns 1 and 2.* Ordered by availability (a,b) and additional criteria (c,d,e,f). Note that the situations described under (b) and (c) fit the present paradigm [17] very well, while they are unsuited to the traditional primeval soup paradigm. A slash between two amino acids indicates that in the early code, no distinction was made between them. *Column 3.* Amino acids added in late stages, in decreasing average order of occurrence in today's proteins [31], implying a decrease in importance. It is noteworthy that other arguments independently suggest the same sequence in which these amino acids were coded for. Prebiotically available Phe and Tyr (b) came first; His, available under special conditions (g) came next; the S-containing Cys and Met (h) followed; and Trp, with no known abiotic synthesis (i), came last; also cf. (j). Criteria: (a) Thermal synthesis involving CH_4, NH_3, and water on quartz sand at 950°C [27]. Concentrations of resulting amino acids decrease from the top to the bottom in table. Similar data from various attempts to simulate prebiotic conditions and from analyses of the Murchison meteorite are compiled in [28]. (b) Thermal synthesis under non-aqueous conditions [27]. Concentrations of amino acids decrease from the top to the bottom. (c) Easily obtained from Glu and Asp but unstable against UV radiation or heat [28], thus absent in a prebiotic soup under steady state conditions but present in a special location in a distinctive environment in which amino acids continuously emerged. Possibly formed from Glu and Asp by amidation after binding to tRNA [15,28]. (d) The abundance of Pro would place it further up in the table by 5 amino acids. However, its steric properties strongly affect the structure of an oligopeptide, and we assume that this fact retards its utilization. (e) Very similar amino acids, same codon at first; later separate codons. (f) Metabolic pathways for generating these amino acids were established early, providing independence from abiotic sources, a fact that supports their early introduction into the code [13]. (g) Synthesis is difficult and requires special conditions [29], thus assumed to occur at a late stage. (h) Sulfur-containing compounds are believed not to be incorporated in early proteins [16]. (i) No abiotic synthesis is known; Trp's occurrence is assumed to depend on the presence of a sufficiently sophisticated metabolism. (j) One of two amino acids that is coded for by a single codon, suggesting a late change of these codons from Ile and 'stop' to Met and Trp. A late use of these codons for met and trp is supported by studies indicating that the tRNAs for Met and Trp were derived from other tRNAs by mutation [30]. Differences between mitochondrial codes and the universal code indicate a relative lack of code conservation, e.g. supporting a late differentiation of Met from Ile and of Trp from stop. This variability in code is related to the simplicity of mitochondria putting them under less selective stress than their hosts. For example in all non-plant mitochondria except in those of coelenterates and lower organisms on the one hand, and echinoderms on the other hand, AUA is used for Met instead of for Ile [15]. Coelenterates branched off the main line of the phylogenetic tree early, echinodermes later. The shift of AUA from Ile to Met took place after the coelenterates had branched off and was conserved in all higher organisms. However, in echinoderms there was a reversal from Met to Ile. (k) Amino acids that occur in present-day proteins with an averaged frequency of 4% or less, in decreasing order. The present-day occurrences in columns 1 and 2 are above 4% [31].

1.		2.		3.	
Gly	(a,f)	Lys	(b)	Phe	(b,k)
Ala	(a,f)	Arg	(b)	Tyr	(b,k)
Asp/Glu	(a,f,e)	Gln/Asn	(c,e)	His	(g,k)
Val	(a,f)	Pro	(a,d)	Cys	(h,k)
Leu/Ile	(a,e)			Met	(h,j,k)
Ser	(a)			Trp	(i,j,k)
Thr	(a)				

The next amino acids are arginine and glutamine/asparagine. We assume that, later in stage D, complementarity in position 3 gradually becomes important again, to increase the number of available codons. However, at first only a Pu/Py complementarity is needed; that is, for a Pu in the codons, there needs to be a Py in the anticodons and vice versa. The code letter for serine, the N in AGN, settles on Py. Thus, Pu is no longer used for serine and AGPu becomes available for arginine. Similarly, AAPy is no longer used for lysine and becomes available for asparagine/glutamine. Moreover, a distinction is made between aspartic acid and glutamic acid, GAPy coding for the former and GAPu for the latter.

Stage E, codons NNN

As the final stage is approached, the Pu requirement for position 1 (for maintaining the reading frame) is relaxed and position 1 gradually can be occupied as well by Py (U or C). However, UPuPu remains reserved for stop codons. This means that CCN, CUN, UCN, UUN, CGN, CAN, UGPy and UAPy become available. The new possibilities are utilized in our model for two purposes: to gain access to amino acids not yet incorporated, and to provide additional codons for important amino acids, perhaps as a protection against excessive mutations and/or to provide a large pool of tRNAs for these amino acids.

Codons CCN and CUN, differing from the stop codons UPuPu at positions 1 and 2, are now available for nonpolar amino acids. CCN codes for proline and CUN for leucine; Pro is prebiotically abundant but has not been pressed into use up to now because its use in oligopeptides presents steric difficulties (it cannot participate in alpha-helical conformations); Leu is the amino acid with the highest frequency in today's proteins [31] and is now supplied with additional codons. Following our polarity assumption, codons UCN and UUN, differing from UPuPu in position 2, are used for weakly polar or nonpolar amino acids. We assign UCN to serine and UUN to leucine. This provides additional codons for both; Ser is also quite prevalent in today's proteins [31]. Codons CGN and CAN, differing from UPuPu in position 1, become available for polar amino acids; CGN (in addition to other codons) is used for arginine and CAN for glutamine (previously not distinguished from asparagine).

Stage F

Once the new codon CAN is used for glutamine, AAPy can code exclusively for asparagine. Similarly, the use of CUN and UUN for leucine permits the restriction of AUN to isoleucine. The availability of codons thus liberated permits amino acids whose prebiotic availability is less certain (Table 1), to be added to the program. We assume that, in position 3 in the codons UUN for Leu and CAN for Gln, Py is not used any more. At this point, the codons UUPy and CAPy become available for new polar and nonpolar amino acids, respectively. We assign the first to nonpolar phenylalanine and the second to polar histidine. For the next amino acids in Table 1, cysteine and tyrosine, the codons UPuPy that differ from UPuPu in position 3 remain. Of these, UGPy is assigned to less polar Cys and UAPy to more polar Tyr [32]. All 64 codons have now been assigned.

Stage G

In this last stage AUN and UPuPu differentiate. Of the four AUN codons for isoleucine, AUG becomes used for methionine, and UGG, one of the four stop codons UPuPu, becomes associated with tryptophan. This brings us to the present-day code.

The approach we have used here reconstructs the modern code through a parsimonious sequence of incremental stages. Each stage is fully plausible and follows known laws of chemistry and physics and rests upon conditions of the stage that preceded it. The insight thus afforded strongly suggests that the ancestral self-replicating system resembled the HA-device.

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