



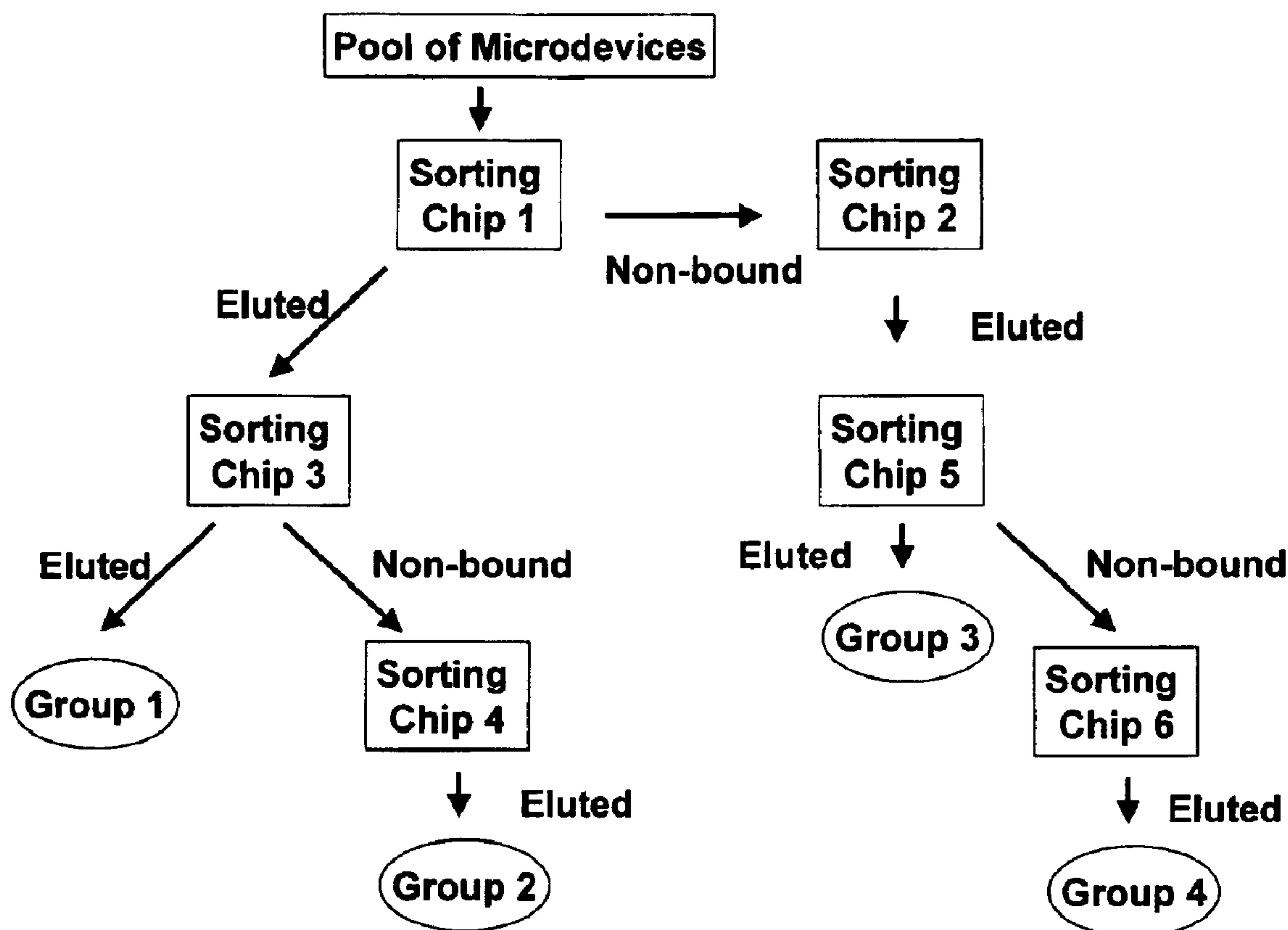
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(54) Title: SORTING OF MICRODEVICES



(57) Abrégé/Abstract:

Particles or other microdevices are disposed in an array having discreet regions (e.g. magnetic bars), oriented within a magnetic field, and then sorted through application of a removing force under conditions that remove a proper subset of the microdevices



(57) **Abrégé(suite)/Abstract(continued):**

from the array as a function of differing orientations of the microdevices. Methods are also contemplated for using magnetic patterns to sort collections of microdevices by magnetic complementarity. Preferred methods use a capture and release process to sort microdevices (microdevices), and unlike conventional sorters, do not require high particle flow rates. Also contemplated are microdevice libraries in which microdevices have mutually distinct magnetic codes, and a region with a mutually distinct polymeric or other chemical moiety.

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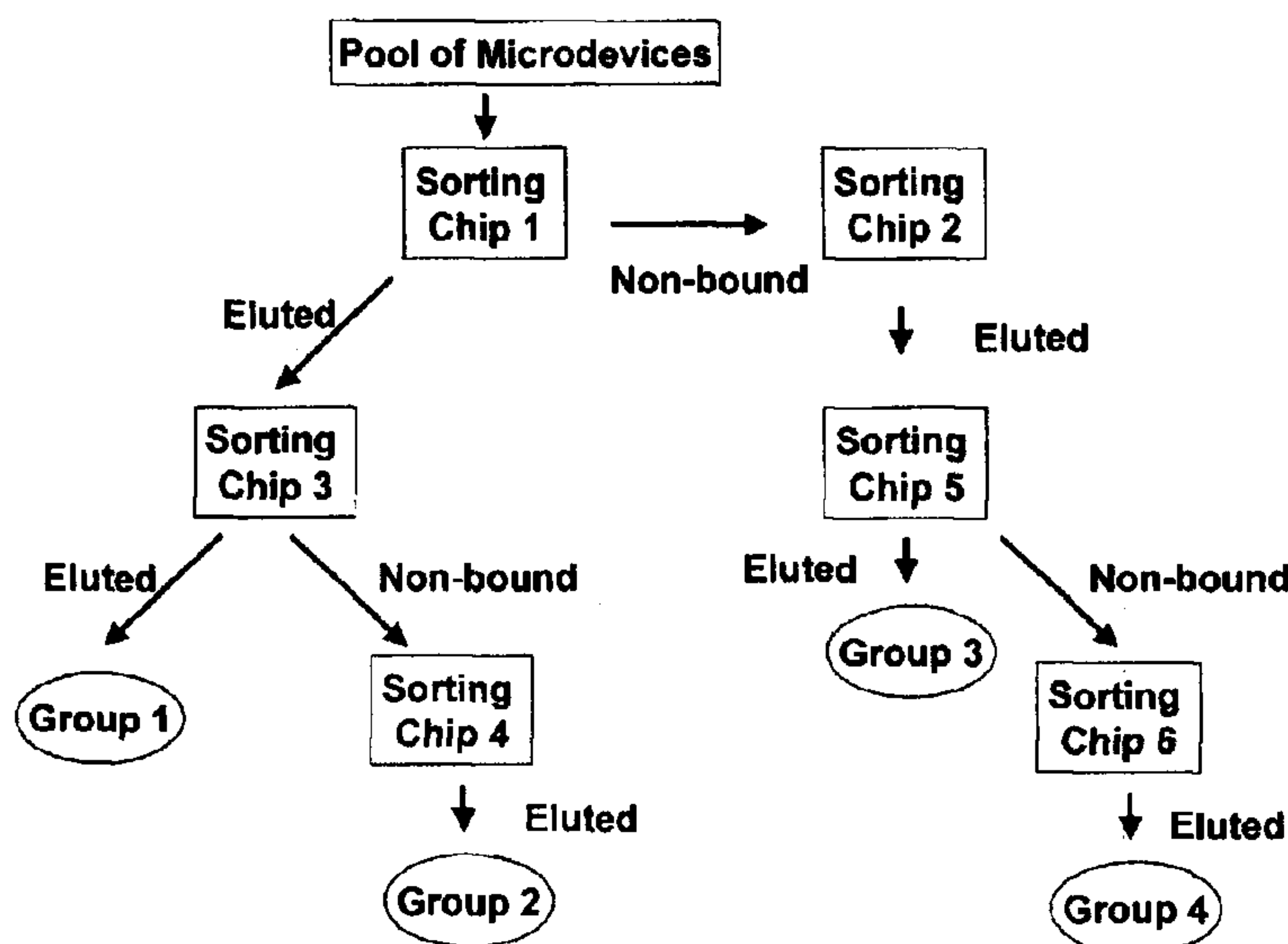
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(54) Title: SORTING OF MICRODEVICES



(57) Abstract: Particles or other microdevices are disposed in an array having discreet regions (e.g. magnetic bars), oriented within a magnetic field, and then sorted through application of a removing force under conditions that remove a proper subset of the microdevices from the array as a function of differing orientations of the microdevices. Methods are also contemplated for using magnetic patterns to sort collections of microdevices by magnetic complementarity. Preferred methods use a capture and release process to sort microdevices (microdevices), and unlike conventional sorters, do not require high particle flow rates. Also contemplated are microdevice libraries in which microdevices have mutually distinct magnetic codes, and a region with a mutually distinct polymeric or other chemical moiety.

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SORTING OF MICRODEVICES

[0001] This application claims priority to US provisional application ser. no. 60/886370 filed January 24, 2007, and to US provisional application ser. no. 60/886373 filed January 24, 2007.

Field of the Invention

[0002] This invention relates to the use of physical forces to sort collections of microdevices into subsets.

Background

[0003] Commonly used particle sorting technology is based on the movement of particles through a device or channel. Sorting rates are dependent on the flow rate of the particles and high flow rates can damage particles. Since sorting particles in a channel narrow enough to direct the flow of the particle is slow and subject to channel blockage, channels typically used are substantially larger in diameter than the particles to be sorted. Consequently sorting processes often involve using electrostatic charge to direct particles to a particular stream – a method not well suited for dense particles. Most systems rely on reading an optical signal (generally fluorescence) to identify particles during the sorting process. While cell and particle sorters are able to achieve speeds on the order of 10^6 particle/min this rate refers to the detection of the particles, separation of particles into high purity fractions is generally ~two orders or more of magnitude slower.

[0004] This application references various patents, patent applications, and publications. The contents of all of these items are hereby incorporated by reference in their entirety. Where a definition or use of a term in a reference, which is incorporated by reference herein is inconsistent or contrary to the definition of that term provided herein, the definition of that term provided herein applies and the definition of that term in the reference does not apply.

Summary of the Invention

[0005] The present invention provides systems and methods in which particles or other microdevices are disposed in an array having discreet regions (e.g. magnetic bars), oriented within a magnetic field, and then sorted through application of a removing force under conditions that remove a proper subset of the microdevices from the array as a function of differing orientations of the microdevices.

[0006] In one aspect of preferred embodiments at least some of the discreet regions can be sufficiently aligned to appear as one or more bands, with another one or more of the regions oriented parallel to, but offset from the band. Adjacent regions can advantageously be separated by an inter region distance of 0.1 to 500 μm . Unless otherwise apparent from the context, all ranges described herein are inclusive of the endpoints.

[0007] Regions preferably contain substantially parallel bars of a magnetized material, which can be permanently or only transiently magnetized. Bars can have any combination of low or high coercivity, and low or high remanence. A given region can contain 1, 2, 3 or an even higher number of such bars.

[0008] A preferred method of sorting comprises the steps of: positioning a set of microdevices on an array; applying a magnetic field to the microdevices in a manner that alters magnetic interactions of a subset of the microdevices with the array; and selectively removing the subset of microdevices from the array. The steps of applying the magnetic force and selectively removing can be advantageously performed at least five times.

[0009] In practice, the arrays can be used to perform combinatorial chemistry. For example, one can provide a plurality of magnetically orientable microdevices, each of which includes an active site having a relatively high chemical reactivity (a "chemically active site"), and each of which includes an individual and optionally unique code; divide the microdevices into at least first and second sets; perform different reactions at the reactive sites of the microdevices in the first and second sets, and then recombining at least portions of the first and second sets of microdevices. The process can be repeated for third and fourth sets, and so forth. In line with the descriptions above, it is especially contemplated that one could at least partially sort at least some of the microdevices as a function of the orientation on an array, using a code that can support 10, 10^3 , 10^6 or even a greater number of choices. It is also contemplated that one could use the step of sorting to facilitate dividing the microdevices from the recombined first and second sets into the at least third and fourth sets.

[0010] Viewed from another perspective, the inventive subject matter can be seen to include methods of using of magnetic patterns to sort collections of microdevices by magnetic complementarity. Preferred methods use a capture and release process to sort microdevices (microdevices), and unlike conventional sorters, do not require high particle flow rates. The density and size of a particle does not interfere with sorting by magnetic complementarity.

Because the sorting can be carried out in a batch process, very high effective rates of particle sorting and separation are achievable – on the order of 10^9 microdevices/min. This is 4-6 orders of magnitude greater than the rates of conventional FACS (Fluorescence Activated Cell Sorting) or flow cytometry-based instruments. Moreover, although some specific applications can benefit from use of an optical reading device, many embodiments of the inventive subject matter do not require use of such a device.

[0011] Contemplated physical embodiments can include the following components:

[0012] 1) A set of magnetically encoded microdevices. Said microdevices comprise a nonmagnetizable substrate and magnetizable material that contain a magnetically distinguishable code. Individual microdevices can range in size from 500 micron to less than 1 micron.

[0013] 2) A sorting chip that, by means of magnetic complementarity, is able to divide a set of microdevices into subsets, comprising bound and non-bound microdevices. Said sorting chip comprises a substrate and a magnetically distinguishable coding region. In a preferred embodiment the sorting chips each contain a plurality of coding regions. A coding region can be substantially identical to its neighboring coding regions or it can be distinct from its neighboring coding regions.

[0014] 3) A magnetic field generator. Said field generator can be electromagnetic or it can include permanent magnets or a combination of the two. Preferred embodiments include electromagnetic generators capable of generating uniform fields over the surface of the sorting chip.

[0015] 4) A force generator for removing non-bound microdevices from the sorting chip. Preferred embodiments include those using fluidic force either alone or in combination with a magnetic force generator.

[0016] The inventive subject matter also includes methods of displaying, comprising: providing a set of microdevices, different ones of which include different magnetic codes; providing an array having a first and second arraying sites that complement different ones of the magnetic codes, adding the microdevices to the array; and applying an external magnetic field to the array such that distinct subsets of the microdevices select to the first and second sites, respectively. Such methods can advantageously include at least an additional eight

arraying sites that complement different magnetic codes from the first and second arraying sites.

[0017] Also contemplated are microdevice libraries that include at least first, second and third microdevices, each of which has a mutually distinct magnetic code, and a region with a mutually distinct chemical moiety. In such libraries the mutually distinct chemical moieties can be polymers (e.g., peptides or nucleic acids) or non-polymers. Still further, the inventive subject matter includes chemical entities that are invented, developed or otherwise researched through use of such libraries.

[0018] For purposes of summarizing the claimed inventions and their advantages achieved over the prior art, certain objects and advantages of the inventive subject matter have been described herein. Of course, it is to be understood that not necessarily all such objects or advantages can be achieved in accordance with any particular embodiment. Thus, for example, those skilled in the art will recognize that the inventive concepts can be embodied or carried out in a manner that achieves or optimizes one advantage or group of advantages as taught herein without necessarily achieving other objects or advantages as can be taught or suggested herein.

[0019] All of the embodiments described herein are intended to be within the scope of the inventive subject matter. These and other embodiments will become readily apparent to those skilled in the art from the following detailed description of the preferred embodiments having reference to the attached figures, the subject matter not being limited to any particular preferred embodiment(s) disclosed.

Brief Description Of The Figures

[0020] Figure 1. **Left panel:** Face up and face down orientations of the same type of microdevice containing 2-bar (each bar having three fingered ends) magnetic code and non-magnetic optical code (OCR characters 437). Magnetic code is located symmetrically within microdevice with respect to the x- and y- axes (the long axes of a microdevice), but asymmetrically located with respect to the z-axis being 1 micron from the bottom surface of the microdevice and 1.8 micron from the top surface of the microdevice. Magnetic elements on arraying chip located 0.46 micron below top surface. **Center panel:** Arrayed mixture of face-up and face down microdevices in the presence of an arraying field parallel to the long

axis of the magnetic bars. **Right panel:** Same view during application of a lifting field (z-axis) that lifts only the face-down microdevices.

[0021] Figures 2A - 2C. A six position coding scheme ($n=6$): A. Enumerated representations for one element ($k=1$) and two element ($k=2$) codes; B. Enumerated representations for three element ($k=3$) code; C. Enumerated representations for four element ($k=4$), five element ($k=5$), and six element ($k=6$) codes.

[0022] Figure 3. Ten pair of three element orthogonal arraying patterns suitable for sorting the coding schemes that are shown in Figure 2.

[0023] Figure 4. Eighteen position code corresponding to three six-position codes. By using three elements ($k=3$) for each six-position code twenty representations for each six-position code can be obtained (as shown in Figure 2B). Such a code can be used to encode a tripeptide library consisting of all combinations of the naturally occurring amino acids.

[0024] Figure 5. A four position coding scheme ($n=4$): Enumerated representations for one element ($k=1$), two element ($k=2$), three element ($k=3$), and four element ($k=4$) codes.

[0025] Figure 6. Examples of asymmetric microdevices. Microdevices comprise either an asymmetrical shape or an asymmetrical arrangement of magnetic elements or both. Magnetic elements may consist of a magnetic code and magnetic alignment elements; in the examples magnetic alignment elements are shown as thicker bars.

[0026] Figure 7. Enumerated representations for microdevices containing an eight position coding scheme ($n=8$) containing five element ($k=5$) codes and asymmetric arraying bars.

[0027] Figure 8. Thirty-five pair of four element orthogonal arraying patterns that are suitable for sorting the microdevices shown in Figure 7.

[0028] Figure 9. Schematic of a multi-split sorting process to produce four sets of microdevices. In the multi-split sorting processes a pool of microdevices is divided into groups and the groups are divided further. In this example the pool is first divided into two subgroups and then each subgroup is then further divided into two groups.

[0029] Figure 10. Schematic of a sequential sorting process to produce four groups of microdevices. In the sequential sorting processes a pool of microdevices is divided into groups in a stepwise manner. In this example the pool is divided into four groups.

[0030] Figure 11. Schematic of a sequential sorting process to produce four groups of microdevices using the minimum number of sorting chips. Microdevices that are unbound after the third sorting step are all members of the same group. Consequently, the final sorting chip in Figure 10 captures all members of the group and is not strictly required.

[0031] Figure 12. Schematic of a multi-split sorting process to produce four groups of microdevices using the minimum number of sorting chips. Microdevices that are unbound after each sorting step are all members of the same group or sub-group. Consequently, three sorting chips in Figure 9 capture all members of the group or sub-group and are not strictly required. Sorting chips are numbered as in Figure 9.

[0032] Figure 13. Schematic of a multi-split sorting process to produce four groups of microdevices wherein each group is captured and eluted from a sorting chip. Sorting chips are numbered as in Figures 9 and 12.

[0033] Figure 14. Fifteen sets of four element orthogonal arraying patterns suitable for sorting the $n=6$ $k=5$ coding schemes shown in Figure 2C into three groups.

[0034] Figure 15. Sixteen position coding space shown as one 8-position code with two arrangements per position (upper representation), two 4-position codes with two arrangements per position (lower representation).

[0035] Figure 16. Enumerated representations for a four position coding scheme ($n=4$, $k=3$, $m=2$).

[0036] Figure 17. Upper panel: 8-position code with two arrangements per position ($n=8$ $m=2$). Lower panel: 8-position code with three arrangements per position ($n=8$ $m=3$). Left side shows general representation with all possible positions filled and right side show specific example of a $k=7$ representation. Magnetic elements are the same size in the microdevices shown in the upper and lower panels.

[0037] Figure 18. Schematic representation of arraying of low coercivity microdevices on a low coercivity arraying chip. Left side shows a pattern of arraying bars on an arraying chip.

Right side shows that same pattern with a microdevice arrayed. Arrow indicates the direction of the external magnetic field.

[0038] Figure 19. Schematic representation of arraying of low coercivity microdevices containing a four position single-element code ($n=4$ $k=1$) on a low coercivity sorting chip. Left side shows a pattern of sorting bars on a sorting chip – all arraying positions are equivalent. Right side shows the same sorting chip with microdevices containing all four codes in arrayed form. Arrow indicates the direction of the external magnetic field.

[0039] Figure 20. Schematic representation of sorting of low coercivity microdevices containing a four position single-element code ($n=4$ $k=1$) on a low coercivity sorting chip. Left side shows microdevices containing all four codes of a four position code arrayed on sorting chip. Right side shows the same arrayed microdevices after application of a magnetic lifting force and removal of the lifted microdevices. Only those microdevices with a code complementary to the sorting chip are retained – selection criterion was one coding element being aligned. Arrow indicates the direction of the external magnetic field.

[0040] Figure 21. Schematic representation of a low coercivity sorting chip where bars in the arrayed microdevice will simultaneously partially and fully overlap bars on the arraying chip.

[0041] Figure 22. Actual representation of a portion of a low coercivity sorting chip where bars in the arrayed microdevice will simultaneously partially and fully overlap bars on the arraying chip. On the right are a pair of microdevices that can be sorted on the sorting chip; the upper microdevice exactly matches the pattern of five bars on the sorting chip, while the lower microdevice only matches two of the bars on the sorting chip.

[0042] Figure 23. Actual representation of a sorting process. Left panel: portion of sorting chip of the type shown in Figures 21 and 22 containing an arrayed mixture of two different microdevices of the type shown in Figure 22; Center panel: same view during application of a lifting field that lifts only one of the microdevices; Right panel: same view after application of fluidic force to remove the lifted (non-bound) microdevice.

[0043] Figure 24. Schematic representation of arraying of low coercivity microdevices on a high coercivity arraying chip. Left side shows a microdevice arrayed when the external field is aligned in parallel with the direction of magnetization of the magnetic elements on the arraying chip. Right side shows a microdevice arrayed when the external field is aligned in

antiparallel with the direction of magnetization of the magnetic elements on the arraying chip. Arrow indicates the direction of the external magnetic field.

[0044] Figure 25. Schematic representation of arraying of low coercivity microdevices containing a 32 position 15-element code ($n=32$ $k=15$; >565 million codes) on a high coercivity sorting chip. Left side shows a pattern of sorting bars on a sorting chip – all arraying positions are equivalent. Right side shows the same sorting chip with microdevices containing a 32-position code arrayed. Arrow indicates the direction of the external magnetic field. External magnetic field is aligned in antiparallel with the direction of magnetization of the magnetic elements on the sorting chip.

[0045] Figure 26. Schematic representation of sorting of low coercivity microdevices containing a 32 position 15-element code ($n=32$ $k=15$) on a high coercivity sorting chip. Left side shows microdevices containing a 32-position code arrayed on sorting chip. Right side shows the same arrayed microdevices after application of a magnetic lifting force and removal of the lifted microdevices. Only those microdevices with a code complementary to the sorting chip are retained – selection criterion was greater or equal to eight coding elements being aligned. Arrow indicates the direction of the external magnetic field.

[0046] Figure 27. Schematic representation of a portion of a high coercivity sorting chip where each arraying position is unique.

[0047] Figure 28. Schematic representation of a portion of a low coercivity sorting chip that contains two different arraying sites. On the right are a pair of microdevices that can be arrayed on the sorting chip.

[0048] Figure 29. Actual representation of a portion of a low coercivity sorting chip that contains two different arraying sites. On the right are a pair of microdevices that can be arrayed on the sorting chip.

[0049] Figure 30. Actual representation of the non-random arraying process showing portion of sorting chip of the type shown in Figures 28 and 29 containing an arrayed mixture of two different microdevices of the type shown in Figure 29.

Detailed Description**Definitions**

[0050] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications referred to herein are incorporated by reference in their entirety. If a definition set forth in this application is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth in this application prevails over the definition that is incorporated herein by reference. In instances where a definition is not set forth in this application and conflicting definitions arise amongst definitions incorporated herein by reference, those definitions given in a co-pending US Patent Application No. 12/018319, entitled "Microdevice Arrays Formed by Magnetic Assembly," filed on even date herewith shall prevail.

[0051] As used herein, "coercivity" of a material refers to the intensity of the applied magnetic field required to reduce the magnetization of that material to zero after the magnetization of that material has been driven to saturation. Coercivity is usually measured in oersted units. A magnetic field greater than the coercivity of a material must be applied to that material in order to coerce it to change the direction of its magnetization. A "high coercivity" material is often referred to as a permanent magnet.

[0052] As used herein, a "predetermined preferential axis of magnetization" means a preferential axis of magnetization that can be predetermined through knowledge of the manufacturing process and design of the microdevice. The "predetermined preferential axis of magnetization" of a microdevice is a fundamental aspect of the design of that microdevice, for example, bar-shaped elements of CoTaZr as used in many of the examples presented in this application have a predetermined preferential axis of magnetization that is parallel to the long axis of the magnetic bar. A "predetermined preferential axis of magnetization" is a property of a microdevice that depends on the geometry, composition, and structural configuration of the magnetic elements of the microdevice. Bar-shaped elements of CoTaZr as used in many of the examples presented in this application have a predetermined preferential axis of magnetization that is parallel to the long axis of the bar; in contrast conventional magnetic beads which have a random distribution of magnetic material do not

have a predetermined preferential axis of magnetization. The induced magnetization along the predetermined preferential axis of magnetization (in its absolute magnitude) is larger than or at least equal to induced magnetization along any other axis of the microdevice. In general, for a microdevice of the present invention to rotate or orient itself under the interaction of the applied magnetic field and the induced magnetization, the induced magnetization (in its absolute magnitude) along the predetermined preferential axis of magnetization of the microdevice should be at least 20% more than the induced magnetization of the microdevice along at least one other axis. Preferably, the induced magnetization (in its absolute magnitude) along the predetermined preferential axis of magnetization of the microdevices of the present invention should be at least 50%, 70%, or 90% more than the induced magnetization of the microdevice along at least one other axis. Even more preferably, the induced magnetization (in its absolute magnitude) along the predetermined preferential axis of the magnetization of the microdevices of the present invention should be at least two, five times, ten times, twenty times, fifty times or even hundred times more than the induced magnetization of the microdevice along at least one other axis. As used herein, an “orthogonal” set of sorting chips divides a space into groups such that through appropriate choice of a magnetic selection criterion all members of a group can be captured (remain bound) by one member of the orthogonal sorting set.

[0053] As used herein, a “bound” microdevice is one that is in an arrayed position during a sorting step on a sorting chip. A “non-bound” microdevice is one that is not in an arrayed position during a sorting step on a sorting chip. During a sorting step an “arrayed” microdevice is one that is held in a position that is substantially parallel to the surface of the sorting chip by magnetic association with the sorting chip. An “eluted” microdevice is one that was a “bound” microdevice at an earlier step in the sorting process but that has become “non-bound”. Bound, non-bound, and eluted refer to processes that occur on a single sorting chip. For example, a collection of magnetically encoded microdevices are placed on a sorting chip and arrayed. A magnetic selection criterion corresponding to a magnetic field is applied resulting in a subset of the microdevices becoming non-bound by being lifted from the surface of the sorting chip and orienting substantially perpendicular to the surface of the sorting chip. These non-bound microdevices are removed using some type of force generator. The remaining bound microdevices are then eluted through application of a magnetic field and/or some type of force generator. As used herein, non-bound refers to the first subset of microdevices removed from a sorting chip during a sorting process while all subsequent

subsets of microdevices removed from a sorting chip are referred to as eluted. In some instances the only non-bound subset corresponds to broken and defective microdevices and may have no members.

Microdevice, Detailed Description.

[0054] The microdevice contains magnetically distinguishable code that enables the microdevice to be sorted. Said microdevice comprises a magnetizable substance and can have a preferential axis of magnetization. Additional features can be incorporated into the microdevice, including, but not limited to, photorecognizable coding patterns. The properties of such microdevices containing photorecognizable coding patterns are enumerated in US Patent 7,015,047. US Patent 7,015,047 discusses a subset of microdevices compatible with the magnetic assembly process.

[0055] The microdevices can have any shape. They can have planar surfaces, but they need not have planar surfaces; they can resemble beads. Flat disks are a preferred implementation. Microdevices shaped as circles, squares, ovals, rectangles, hexagons, triangles, and irregular shapes are all amenable to the magnetic assembly arraying process. The microdevices can be of any suitable dimension(s). For example, the thickness of the microdevice can be from about 0.1 micron to about 500 microns. Preferably, the thickness of the microdevice can be from about 1 micron to about 200 microns. More preferably, the thickness of the microdevice can be from about 1 micron to about 50 microns. In a specific embodiment, the microdevice is the form of a rectangle having a surface area from about 10 squared-microns to about 1,000,000 squared-microns (e.g., 1000 micron by 1000 micron). In another specific embodiment, the microdevice is an irregular shape having a single-dimension from about 1 micron to about 500 microns.

[0056] The microdevices can contain one or many magnetizable elements. The microdevices can have a predetermined preferential axis of magnetization.

[0057] The individual magnetic elements within the microdevice can be of any width, length, thickness and shape. The individual magnetic elements within a microdevice can be composed of different materials having similar or different magnetic properties.

[0058] Any suitable magnetizable material can be used in the present microdevices. In one example, the magnetizable substance used is a paramagnetic substance, a ferrimagnetic

substance, a ferromagnetic substance, or a superparamagnetic substance. Preferably, the magnetizable substance is a transition metal composition or an alloy thereof such as iron, nickel, copper, cobalt, manganese, tantalum, and zirconium. In a preferred example, the magnetizable substance is a metal oxide. Further preferred materials include nickel-iron (NiFe) and cobalt. Additional preferred materials include alloys of cobalt such as CoTaZr, cobalt-iron (CoFe), cobalt-nickel-iron (CoNiFe), cobalt-niobium-zirconium (CoNbZr), cobalt niobium hafnium (CoNbHf), and cobalt tantalum hafnium (CoTaHf). Preferably such features are bar shapes that have a preferential axis of magnetization. The term "bar", in addition to rectangular shapes, includes rod-like shapes as well as slightly irregular shapes that still exhibit a preferential axis of magnetization, e.g., elongated pyramidal shapes. A bar need not be solid and can contain cutouts or holes as described below. The magnetizable substance can be situated completely inside (encapsulated) the non-magnetizable substrate comprising the microdevice, completely outside yet attached to the non-magnetizable substrate comprising the microdevice, or anywhere in between. Preferably the magnetizable substance is patterned, for example using micromachining or lithographic techniques, so that its three-dimensional shape is a known feature of the design of the microdevice.

[0059] Because the microdevices are used to carry out assays in a liquid array format, it is advantageous that they can be conveniently aliquoted or dispensed using conventional liquid and bead handling devices (e.g. pipettors). Consequently, it is desirable that they do not self-associate in the absence of a magnetic field. Therefore, low remanence (i.e., magnetization left behind in a medium after an external magnetic field is removed) is a desirable quality. Cobalt alloys such as CoTaZr and iron oxides (Fe_3O_4) are preferred examples of magnetic materials that meet this criterion.

[0060] In a preferred embodiment, microdevices include a non-magnetic substrate composed of multiple layers, as described in US Patent 7,015,047. This non-magnetic substrate can contain other features including optical encoding patterns and wells. Additional features can be included and any of the wide range of features compatible with planar microfabricated devices such as those used in Micro-Electro-Mechanical Systems (MEMS) can be incorporated into the non-magnetizable substrate of the microdevice. In a preferred embodiment the microdevice contains electrical contact pads and circuitry that allow MEMS type sensors within the microdevice to be utilized. This circuitry is composed of electrically conductive material that is preferably encapsulated within the substrate of the microdevice

such that only contact pads and sensor elements are exposed on the surface of the microdevice. Contact pads on the surface of the microdevice can be used to connect the microdevice to a power source(s) and/or sensing device(s) by means of complementary contact pads on the arraying chip. In a preferred embodiment, electrical circuitry is placed within each microdevice in a unique configuration, thus the connection between the microdevice contact pads and the complementary pads on the arraying chip may be used to determine the identity of the microdevice.

[0061] In one embodiment the microdevices comprise a chemically reactive surface that is suitable for attachment of a chemical or biological moiety. In another embodiment this surface is present in a well or indentation. In one embodiment this surface is produced by means of a silane (e.g. aminopropyltrimethoxysilane, gycidoxypopyltrimethoxy silane). In another embodiment a reactive surface is produced by means of a thiol containing reagent (e.g. 11-mercaptoundecanoic acid). In another embodiment the reactive surface is a self-assembled monolayer (for example as reviewed in "Formation and structure of self-assembled monolayers" by Ulman Chem. Rev. 96:1533-1554 (1996) and "Self-assembled monolayers of thiolates on metals as a form of nanotechnology" by Love et al. Chem. Rev. 105:1103-1169 (2005)). The reactive surface can be generated on the microdevice using batch techniques (e.g. a set of microdevices placed in an aqueous solution of the appropriate reagent, such as silane to generate a reactive surface on exposed silicon dioxide surface of the microdevice). Alternatively, the reactive surface can be generated on the microdevices prior to their release from the wafer (during or after the fabrication process). The reactive surface can be applied to all the microdevices on the wafer (e.g. by gas or liquid phase silanization) or at particular positions on the wafer using position specific deposition (e.g. inkjet) or masking (e.g. photolithography) such that the reactive surface is applied only to a subset of microdevices on the wafer or even to specific locations on individual microdevices. In a further embodiment such position specific processes can be used to produce unique chemical compounds on individual microdevices. Such techniques are widely used to produce DNA microarrays and are well-established art (e.g. "Spatially addressable combinatorial libraries" by Pirrung Chem. Rev. 97, 473-488 (1997) and "In situ synthesis of oligonucleotide microarrays" by Gao et al. Biopolymers, 73:579-596 (2004)). In a further embodiment the locations of reactive surface on individual microdevices can be patterned. Such patterning can be generated by masking in which a material is used to protect a surface from being modified, for example a layer of photoresist can be used to surround a silicon dioxide well

and then following the silanization of the well surface the photoresist can be dissolved away to reveal a unsilanized surface. Patterning can also be achieved through the use of different materials, for example a gold surface can be created on a silicon dioxide surface, reaction with a carboxylated alkyl thiol will yield a carboxylated surface only over the gold. Individual microdevice can contain one or many patterned reactive surfaces. Such methods are well established in the fabrication and chemical literature particularly as applied to the manufacture of DNA and protein microarrays. In additional embodiments the chemically reactive surface corresponds to a linker molecule used in solid phase synthesis. Many such linker molecules are known to those practiced in the art of combinatorial chemistry (e.g. as referenced in Jung, G., *Combinatorial Chemistry*, Weinheim, Wiley-VCH, 1999; "Comprehensive survey of chemical libraries for drug discovery and chemical biology; 2006" by Dolle et al. *Journal of Combinatorial Chemistry*, 9:855-902 (2007)).

[0062] When a microdevice that contains magnetic elements is placed in an external magnetic field, a magnetic dipole(s) is induced in the microdevice. Because the microdevice has a preferential axis of magnetization it will, unless impeded, rotate so as to align its preferential axis of magnetization with the force lines of the external magnetic field. When placed in a rotating external magnetic field the microdevices, unlike conventional magnetic beads, will rotate and, in effect, serve as mini stir-bars. Consequently it is desirable, apart from any considerations with respect to arraying, that the microdevices respond strongly to external magnetic fields. Magnetic elements composed of materials with high saturation magnetizations such as CoTaZr alloys are a preferred embodiment.

Sorting Chip, Detailed Description.

[0063] The sorting chip is comprised of both magnetic and non-magnetic material. A sorting chip performs its function by first arraying microdevices and as such is a specialized arraying chip – the properties and features of general arraying chips are described in a co-pending US Patent Application No. 12/018319 entitled "Microdevice Arrays Formed by Magnetic Assembly," filed on even date herewith and can be applied to the sorting chips disclosed here. Any suitable magnetizable material can be used in the sorting chip. In one example, the magnetizable substance used is a paramagnetic substance, a ferromagnetic substance, a ferrimagnetic substance, or a superparamagnetic substance. Preferably, the magnetizable substance is a transition metal composition or an alloy thereof such as iron, nickel, copper, cobalt, manganese, tantalum, and zirconium. In a preferred example, the magnetic substance

is a metal oxide. Further preferred materials include NiFe and cobalt. Additional preferred materials include alloys of cobalt such as CoTaZr, CoFe, CoNiFe, CoNbZr, CoNbHf, and CoTaHf. Preferably such features are bar shapes that have a preferential axis of magnetization. In many applications residual magnetization in the sorting chip is a desirable quality. Similar to the microdevice, the magnetizable substance in the sorting chip can be situated completely inside (encapsulated) the non-magnetizable substrate comprising the sorting chip, completely outside yet attached to the non-magnetizable substrate comprising the sorting chip, or anywhere in between. A preferred embodiment places the magnetic elements on top of a glass substrate and encapsulates them with silicon dioxide such that the silicon dioxide forms a planar or substantially planar surface. A further preferred embodiment places the magnetic elements on top of a silicon substrate and encapsulates them with silicon dioxide such that the silicon dioxide forms a planar or substantially planar surface.

[0064] Although the examples presented in this application use a sorting chip containing CoTaZr bars that have low remanence and low coercivity, these properties are not necessary for the assembly of magnetic arrays or the sorting process. Since high remanence will cause microdevices to magnetically assemble into chains or clumps in the absence of an external magnetic field, in general, it is not desirable for the microdevices to contain such; although, it can be desirable that the magnetic elements contained within the sorting chip have said qualities in order to allow assembled arrays to remain intact once the arraying field is removed.

[0065] The individual magnet elements within the sorting chip can be composed of different designs. The magnetic elements can be of any shape and size. Individual magnetic elements can be distinct from all other elements or comprise a subset of such elements. The individual magnetic elements can be composed of different materials having similar or different magnetic properties. Preferably the magnetic elements are bar shapes that have a preferential axis of magnetization. More preferably the magnetic elements have a predetermined preferential axis of magnetization. The term "bar", in addition to rectangular shapes, includes rod-like shapes as well as slightly irregular shapes that still exhibit a preferential axis of magnetization, e.g., elongated pyramidal shapes. A bar need not be solid and can contain cutouts or holes.

[0066] A preferred embodiment is magnetic elements that are bars composed of a high permeability ferromagnetic material. These bars can be rectangular or substantially

rectangular. Bars containing “fingers” such as those shown in Figure 1 and described in US Patent 7,015,047 are another preferred embodiment. These fingers can be short (e.g., 1-2% of the total length of the bar) or long (e.g., comprising almost the entire length of the bar) or anywhere in between.

[0067] The non-magnetizable substrate can be comprised of any suitable material including silicon, silicon dioxide, silicon nitride, plastic, glass, ceramic, polymer, metal (e.g., gold, aluminum, titanium, etc.) or other similar materials or combinations of such materials. In a preferred example the material is silicon dioxide. In another preferred example the material is glass. The substrate can comprise a single layer or it can comprise multiple layers. The sorting chip substrate can, but need not be, planar or substantially planar. There can exist indentations in the sorting chip that allow for “seating” of the microdevices to assure exact alignment of said microdevices, which can be desirable for some applications. These indentations, for example, can have planar faces for seating of microdevices that are flat-ish, or they can be spherical for seating of beads or bead-like microdevices. In one preferred embodiment the indentations are designed to match the shape of individual planar microdevices, e.g. rectangular wells to hold rectangular microdevices.

[0068] The number of arraying sites per unit area is dependent on the size and spacing of the magnetic elements on the sorting chip. For example, sorting chips that are arraying microdevices of the size shown in Figure 1 that are 60x75 micron in size can array approximately 100 microdevices per square millimeter. In other embodiments the density will be much higher. For example, microdevices that are 20x25 micron in size can be arrayed and sorted at a density of approximately 1,000 microdevices per square millimeter.

[0069] The sorting chip can contain additional features that are not necessarily required to facilitate the sorting process. Any of the wide range of features compatible with planar microfabricated devices can be incorporated into the non-magnetizable substrate of the sorting chip, such as those used in MEMS (for example as reviewed in Liu, C., *Foundations of MEMS*, Pearson Prentice Hall, Upper Saddle River, NJ, 2006; Gad-el-Hak, M., *MEMS (Mechanical Engineering)*, CRC Press, Boca Raton, 2006). A preferred example is microchannels. Such channels can be used to deliver and/or remove reagents and other materials such as microdevices from the sorting chip surface. Additional preferred examples include electronic and optical microsensors including those used in MEMS (for example as

reviewed in Gardner, J.W. et al., *Microsensors, MEMS, and Smart Devices*, John Wiley & Sons, West Sussex, 2001).

[0070] The magnetic elements of the sorting chip should be complementary to those of the microdevice, but need not exactly match those of the microdevice in dimension or shape.

Fabrication

[0071] Microdevices and sorting chips may be fabricated using any of a variety of processes. In preferred embodiments they are produced using variations of conventional micromachining and semiconductor fabrication methods. Such methods are described and referenced in US Patent 7,015,047 and US Patent Application 2002/0081714 as well as in reviews and textbooks that discuss photolithographic or MEMS fabrication techniques (for example in Banks, D., *Microengineering, MEMS, and Interfacing: A Practical Guide*, CRC Press, 2006).

Distinguishable Magnetic Codes

[0072] Magnetically encoded microdevices contain magnetically distinguishable codes that enable the microdevices to be sorted. A magnetically distinguishable code is a code that can be distinguished from another by magnetic means. Magnetically distinguishable codes differ in the strength and or distribution of their magnetic materials. Preferred embodiments include the distribution of magnetic elements within a substrate. Such distributions can occur along any axis (x, y, or z, where the x-axis is the long axis of the microdevice (length), the y-axis is the second longest axis of the microdevice (width), and the z-axis is the short axis of the microdevice (height)). Figure 1 shows an example of how microdevices that contain magnetic elements that differ only in the placement of those magnetic elements along the z-axis of the microdevice can be distinguished. In that example, arrayed microdevices containing magnetic bars are subjected to a magnetic arraying field that is parallel to the long axis of the magnetic bars in the arraying chip. A second magnetic field perpendicular to the plane of the arraying chip is then provided. Face-up microdevices that have their magnetic elements 1.46 micron from the magnetic elements of the arraying chip; by contrast face-down microdevices have their magnetic elements 2.26 micron from the magnetic elements of the arraying chip. This difference in distance results in a difference in magnetic force between the arraying chip magnetic elements and the face-up and face-down microdevices that is

sufficiently large such that face-down microdevices can be selectively lifted from arraying chip surface by magnetic means.

[0073] Magnetic codes can comprise only a single element and still be distinguishable (e.g. a single bar magnet encapsulated by 1 micron of silicon dioxide can be distinguishable from a single bar magnet encapsulated by 1.1 micron of silicon dioxide when arrayed on an arraying chip of the type shown in Figure 1). Similarly if the microdevice docking location on the sorting chip restricts the motion of a properly docked microdevice (e.g. with a well or posts) then a single element code in the x,y plane can also be distinguishable. Moreover, single element codes that differ in the size, shape, and material comprising the magnetic element can be distinguishable.

[0074] Magnetic elements that form the codes do not need to be uniform in size so long as there is a discrete difference between the magnetic force of a properly arrayed microdevice containing a code to be retained and a properly arrayed microdevice containing a code to be removed in the unbound fraction, such that an appropriate threshold exists for lifting the unbound microdevice while retaining the bound microdevice.

[0075] A preferred embodiment is that the differences in distribution of magnetic material for distinguishable codes reside within the x,y plane of the microdevice. Exemplarily representations of such codes include barcodes. Two primary components of the barcode design processes are the number of codes and the manner in which they can be divided.

Coding Space

[0076] The total number of codes encoded by a space n containing k elements is defined in eqn 1.

$$(1) \text{ Coding Space} = \frac{n!}{k!(n-k)!}$$

[0077] For example, consider a bar code with 6 available positions in the code as shown in Figure 2. This corresponds to n=6 in eqn 1. There are 6 possible values of k. For k=1 there are 6 possible codes; for k=2 there are 15 possible codes; for k=3 there are 20 possible codes; for k=4 there are 15 possible codes; for k=5 there are 6 possible codes; for k=6 there is only one possible code. In order to divide all the codes into orthogonal groups some subset of bars must be used for capture. For k=1 the coding space can be divided in 2,3,4,5, or 6 groups,

since any combination of orthogonal capture bars can be used as shown in Figure 2. For example, consider two orthogonal capture groups each member containing three bars as shown in Figure 3. Each coded microdevice has either one or zero bar overlap with each capture chip – if it has one bar overlap with one capture chip it will have zero overlap with the other members.

[0078] For $k=2$ the situation is more complicated. Using capture bars divided into two orthogonal groups of the type shown in Figure 3, each coded microdevice has two, one, or zero bar overlap with the capture chip. For any given pair there will be only 6 microdevice codes that will have two bar overlap and 9 codes that will have only a one bar overlap and thus fail to be distinguishable. One can always sort using a trivial solution, i.e. arraying patterns that precisely match only one code and such an approach can be of great value as discussed below.

[0079] For $k=3$, again using the capture bar sets shown in Figure 3, each coded microdevice has three, two, one, or zero bar overlap with the capture chip. However, unlike the $k=2$ example, there is no way to evenly divide three bars, consequently for any capture pair every code will have at least 2 bars overlap with only one member of an orthogonal capture pair. Therefore, a capture (selection) criterion of 2 or more bar overlap can be used to evenly divide the coding space.

[0080] For $k=4$ each coded microdevice has three, two, or one bar overlap with the capture chip the same problem exists as for $k=2$, there are 9 codes that will be indistinguishable using any capture criterion (two bars overlap with each member of a capture pair).

[0081] For $k=5$ each coded microdevice has three or two bar overlap. There is no way to evenly divide five bars consequently for any capture pair every code will have 3 bars overlap with only one member of an orthogonal capture pair. Therefore, a capture criterion of 3 bars overlapping can be used to evenly divide the coding space. For $k=6$ there is only one code.

[0082] There are other ways of dividing a coding space other than into two equal groups and coding spaces can be selected so as to tailor the sorting space to meet the specific application. One simple example is peptide synthesis. If one desires to produce all combinations of naturally occurring tri-peptides this requires 8000 codes and the ability to split the microdevices into 20 groups (one for each of the naturally occurring amino acids). Figure 4 shows one method of encoding such a process by using three separate codes for 20 ($n=6$ $k=3$).

The selection criterion becomes the individual representations for each code. This is one of the powerful uses of the “trivial solution” mentioned above. By combining easily divisible codes a large easily assigned coding space can be generated.

[0083] For example consider coding spaces targeted towards DNA synthesis where splitting into four groups is desired. It can be carried out using the same approach as the previous example by using multiple copies of a four member code (e.g. $n=4$, $k=1$ or $n=4$, $k=3$) as shown in Figure 5.

[0084] The codes that have been shown thus far have been numbered for easy identification. However, the patterns shown are symmetrical and as such some codes can not be distinguishable from other codes after rotation, thereby reducing the number of distinguishable codes available for a given coding space. Should it be desired to use the coding space in a more efficient manner, there are a number of ways to overcome symmetry. Several examples are shown in Figure 6. These examples illustrate the use of different patterns of alignment bars that are asymmetrical. While the alignment bars shown in Figure 6 are the bars of greater width this need not be the case and alignment bars that are similar in width to magnetic code elements can be used. Alternatively, if an arraying process is carried out in a well that is complementary in shape to the microdevice then asymmetrical shaped microdevices can be used to eliminate symmetry in the code. It is the overall symmetry of the microdevice that is at issue. Consequently, a symmetrical code and a symmetrical shape can yield an asymmetrical microdevice if none of the symmetry planes and axes of the code and the shape are coincident. Figure 6 shows several asymmetric microdevices. These examples are illustrative and are in no way exhaustive. In a preferred embodiment the microdevices will contain an alignment bar. Alignment bar placement can occur at any position within the microdevice. In another preferred embodiment the microdevices contain asymmetric alignment bars. In a further preferred embodiment the microdevices will contain both an alignment bar and an asymmetric shape. While Figure 6 shows asymmetrical arrangements of codes in the x,y plane, asymmetrical arrangements can also be generated through the asymmetric arrangement of magnetic bars along the z-axis (height of the microdevice) as in the microdevice shown in Figure 1.

[0085] For simplicity in further schematic examples when displaying magnetic codes within microdevices an asymmetric pair of alignment bars will be used.

[0086] The examples given thus far have been straightforward to encode and sort but they do not most effectively utilize the space. In general, for sorting applications where the entire space is to be divided into equal size groups it is usually simplest to have the total number of positions (coding space) in the magnetic code be even (divisible by two) and the number of occupied positions (elements) in the code be odd as this guarantees that the total number of codes can be evenly divided using two orthogonal (non-overlapping) arraying-based sorting steps as demonstrated above for the exemplary coding spaces $n=6, k=3$ and $n=6, k=5$.

[0087] Consider $n=8$, there are a large number of ways to encode and sort an 8 position matrix code – the maximum number of codes is $8!/4!4!$ or 70 by choosing any 4 bars out of the 8 rather than restricting the position to one bar in every four positions. Sorting such a representation into two equally sized orthogonal groups using a unique code is more complex, since as discussed above k is even. The $n=8$ coding space can be divided into two $n=4$ spaces or four $n=2$ spaces each of which would contain 16 unique codes. However, consider another example choosing 5 bars out of 8 this yields 56 codes and since the value of k is odd it is easily divided into two equal sized groups. Figure 7 shows the exhaustive enumeration of this representation, which for convenience of referral have been denoted numerically 1-56. To array these coded microdevices into two equal groups, magnetic arraying bars consisting of 4 bars can be used. Microdevices that have at least three bars magnetically aligned with the sorting chip will be bound while the remaining microdevices will be eluted. For the exemplary coding space shown in Figure 7 there are 35 unique pairs of 4 bars that can be used. Figure 8 shows the possible orthogonal arraying bar patterns for dividing the entire coding space into two groups. Table 1 shows the complete representation of a splitting process for each pair of orthogonal four arraying bar sets.

[0088] Each group can then be subdivided by repeating a sorting process with a different orthogonal set. Consequently, to divide any given space into four groups using 3 pairs of orthogonal sets would require a total of 6 sorting steps as shown schematically in Figure 9. However, when dividing a space into groups it is not strictly necessary to carry out the final step since those microdevices that remain after the next-to-last step are all members of the same group. Consequently the final splitting step is not really a splitting step as it captures all members of the target group. For example when dividing a group into four, as shown in Figure 10, only the first three steps are strictly necessary as shown in Figure 11. Similarly, when using sets of sorting chips that divide the space into two groups, only three steps are

strictly required, as shown in Figure 12. Therefore to divide a group of microdevices into four groups, the multi-split sorting method and the sequential sorting method each only require three sorting steps. There can be, however, an advantage in retaining the final step since it removes any microdevices that should have been captured in the previous step as well as removing any damaged or defective microdevices. A multi-split sorting process can still maintain this quality control process with only five steps. Such a preferred embodiment is shown in Figure 13.

[0089] Comparing a simple sequential sorting approach to a multi-split sorting approach to produce a set of all possible 10-mer oligonucleotides (using A,C,T,G) - this requires 1,048,576 codes (4^{10}). Using a four code approach could use a code space of 40 and 40 sorting steps. Using a multi-split sorting approach could use a coding space of at least 23 ($n=23$ $k=11$ encodes 1,352,078 patterns) and 50 sorting steps. The appropriate choice of coding depends on the specific application.

[0090] There are a variety of other coding options that could be used that permit a space to subdivided in a manner that allows sorting. This can involve choosing a subset of the larger space – the example shown above in Figure 4 of three sets of $n=6$ $k=3$ represents a subset of the $n=18$ $k=9$ space. It can also involve picking a particular selection criterion – there are a wide range of orthogonal sets of arraying chips that can be used. For example, in Figure 2C the $n=6$ $k=5$ group can be divided into two equal groups by using the orthogonal pairs shown in Figure 2C where the selection criterion is using three bars to select three bars. However, the same coding space can be divided into three equal groups by using four bars to select four bars as shown in Figure 14. This example also demonstrates that while the sorting process divides the space into three orthogonal groups the sorting chips within each set each have two elements in common with any other member of the set.

[0091] A coding space can also be divided into more complex coding schemes. One such example is more readily described by rearranging the spacing such that each position is depicted as a column where each column contains more than one possible arrangement of elements; the number of element arrangements per column is denoted by the letter m . The examples shown in Figure 15 illustrate a 16 bar code containing either $n=8$ $m=2$ or two sets of $n=4$ $m=2$. The total number of codes is defined in the following equation:

$$(2) \text{ Coding Space} = \frac{n!}{k!(n-k)!} m^k$$

[0092] For a given value of n and m there are a range of values of k that can be used. For simplicity consider the lower panel in Figure 15 showing two sets of $n=4$ $m=2$. In order to easily split the microdevices into four groups, $k=1$ can be used leading to 64 codes. However, $k=3$ is equally effective at subdividing the space into four groups and leads to a 16-fold increase in the coding space, i.e. 1024 codes. Figure 16 shows the 32 coding patterns for an $n=4$ $m=2$ $k=3$ coding representation.

[0093] One of the advantages of coding representations such as those shown in Figures 15 and 16 is that they can more effectively utilize space. Since only one bar in a column will be used there is no need for there to be a space between the bars and in fact the positions can have considerable overlap. Consequently, in the space of a fully independent 16 element code as shown in Figure 15 could contain 24 elements of the same size as shown in Figure 17. The corresponding $n=8$, $k=7$, $m=3$ representation would result in 17496 codes. This is 36% more codes than the $n=16$ $k=8$ representation and over 50% more than the sorting friendly $n=16$ $k=7$ representation. Formally, the $n=8$, $k=7$, $m=3$ representation is a subset of the $n=24$ $k=7$ representation.

[0094] In a preferred embodiment the patterns include a common set of alignment bars on all microdevices, such that all microdevices whatever their code will array on the sorting chip. While a sorting process can be performed using more than one pattern per sorting chip a preferred embodiment is to use only a single code per sorting chip such that all arraying positions on the sorting chip are equivalent. This results in arraying processes reducing to the robust arraying processes described in a co-pending US Patent Application No. 12/018319, entitled "Microdevice Arrays Formed by Magnetic Assembly," filed on even date herewith.

[0095] The arrangement of magnetic elements on the sorting chip is dependent on the magnetic properties of the magnetic elements on the sorting chip and the magnetic properties of the magnetic elements of the microdevices. A preferred embodiment for microdevices is that their magnetic elements have low coercivity and low remanence so that they will not strongly self-associate in the absence of an external magnetic field. For microdevices of this type, sorting chips containing a wide range of magnetic materials can be used. One preferred embodiment is that the magnetic elements in the sorting chips have low coercivity. To array and sort microdevices on sorting chips with these type of elements, magnetic overlap can be

used, where the North seeking poles overlap South seeking poles. Figure 18 shows a schematic example of a magnetic bar arrayed using such bars. Figure 19 and 20 show schematic examples of a sorting process using low coercivity elements for a $n=4$ $k=1$ encoded microdevice with asymmetrical alignment bars.

[0096] Apart from any consideration of overall magnetic strength, the length of the bars on the arraying chip relative to the length of the bars in the microdevices can be important. Since the “magnetic charge” is concentrated near the ends of the magnetic regions, for low coercivity sorting chips the interaction between fully overlapping bars is repulsive. However in the case of the overlap between a long and a short bar the interaction can be attractive especially when the short bar overlaps the central region of the long bar. The ability of long bars to have favorable magnetic interactions when overlapping with much smaller bars can be used to create arraying chip patterns that increase the overall strength of desirable arraying interactions and improve the efficiency of arraying and sorting. In this procedure a magnetic bar of an arrayed microdevice fully overlaps a smaller bar while still engaging in favorable interactions by partially overlapping two other bars. In a preferred embodiment the fully overlapped bar on the array is less than 50% of the length of the overlapping bar on the arrayed microdevice. In a preferred embodiment the sorting chips contain alternating large and small bars. In a further preferred embodiment the small bars are less than 60% of the gap between the larger bars. Figure 21 shows a schematic example of a sorting chip containing magnetic bars that are smaller than the magnetic bar on the microdevice to be arrayed. Figure 22 shows an actual example of a sorting chip and microdevices that can be sorted using this type of bar pattern. In this example the sorting chip corresponds exactly to one of the microdevices while the other microdevice has only two out of its five magnetic elements in common with the sorting chip. Consequently, a selection criterion of 3, 4, or 5 aligned magnetic elements can be used to distinguish these microdevices. The microdevices are 60x75x3 micron in size. Figure 23 shows an example of these microdevices being sorted. The left most panel of Figure 23 shows a portion of the sorting chip containing each of the type of microdevices in Figure 22 in arrayed form. After application of a lifting field the noncomplementary microdevice is raised from the surface as shown in the central panel. Application of fluidic force (supplied by means of a laboratory micropipettor) removes the raised microdevice (removes the non-bound microdevice as represented in Figures 9-13). The bound microdevice can then be “eluted” as represented in Figures 9-13 by increasing the lifting field and the application of fluidic force to complete the sorting step.

[0097] Another preferred embodiment is that the magnetic elements in the sorting chips have high coercivity. To array and sort microdevices on sorting chips with these type of elements, magnetic overlap can be used. Unlike the magnetic overlap that occurs between low coercivity magnetic elements, magnetic overlap between a low coercivity magnetic element and a high coercivity magnetic element is dependent on the specific direction on the external magnetic field. Figure 24 shows a schematic example of a magnetic bar arrayed using such bars with the external field running parallel and anti-parallel to the direction of the magnetization of the high coercivity elements.

[0098] For high coercivity elements there is no need for gaps to be present in order to array and sort. A preferred embodiment is an arrangement of magnetic elements arranged so as to provide no well-defined gaps between elements. Figures 25 and 26 demonstrate a microdevice being sorted where the microdevices and sorting chips meet this criterion. In this example the coding space ($n=32$, $k=15$) can contain over 565 million different codes, but a single sorting chip can be used to effectively divide the microdevices into two groups of known composition.

[0099] The examples above are in no way intended to be limiting. Sorting does not need to be into equal sized groups. In addition, the same criteria do not need to be used in successive sorting cycles. For example, a first selection could include a set of three bars being used to select all microdevice patterns containing those bars, while a second selection step could correspond to 4 bars requiring perfect matching or even 5 bars selecting for all combinations containing 3 or more bars. A coding space can be sub-divided in a wide variety of ways as will be readily apparent to one skilled in the art. Moreover, a single sorting chip can be used to divide a space by sequentially eluting microdevices. Such a sequential elution process involves eluting in succession more weakly held microdevices. For example, in a code containing 5 magnetic elements such as that shown in Figure 7 the microdevices could be eluted into four separate groups from a single 4-element sorting based on the number of bars that overlap (1, 2, 3, or 4). For example such sequential elution procedures could be used to isolate a specific code using a small number of sorting chips.

[00100] It is also possible to target a single microdevice for elution by generating a localized lifting field such that only one microdevice or a small number of microdevices in the region of the lifting field will be eluted. This can be done using a small electromagnet or a small permanent magnet. Under high-density arraying conditions it is possible that more than

one microdevice will be lifted, but the eluted microdevices can be re-arrayed at lower density and the process repeated to isolate the microdevice of interest. Additionally, sequential elution and localized lifting fields can be used in combination to rapidly isolate an individual microdevice.

Non-Random Arraying

A sorting process can be performed using more than one pattern per sorting chip. In that situation microdevices will be directed to array through magnetic complementarity to specific locations on an arraying chip. In one embodiment the array contains a subset of the magnetic codes and selection criteria can be used to select the subset of microdevices that will be retained at a particular array location. In another preferred embodiment the arraying chip contains a unique pattern of magnetic elements corresponding to each magnetic coded microdevice. Such particle arrays are no longer random as the location of specific coded microdevice on the arraying chip is determined by the location of its complementary magnetic pattern. Figure 27 shows a schematic diagram of such an array on a high coercivity arraying chip with each arraying position being unique. Figure 28 shows a schematic example of a much simpler low coercivity arraying chip in which two different arraying patterns are being used as well as two microdevices that can be arrayed on such as an array. Figure 29 shows an actual example that corresponds to the schematic example in Figure 28. The microdevices are 60x75x3 micron and contain 5 magnetic elements that are 50x3x0.4 micron. Figure 30 shows an actual non-random array formed using the microdevices and arraying chip shown in Figure 29. Microdevices are only arrayed in the locations on the array that fully match their magnetic codes.

Magnetic Field Generator

[00101] A magnetic field generator can be electromagnetic, or it could include permanent magnets, or a combination of the two. Preferred embodiments include electromagnetic generators capable of generating uniform fields over the surface of the sorting chip

[00102] The external magnetic field generators can also be electromagnetic, or it can include permanent magnets, or a combination of the two. The initial step in a sorting process is the arraying of the microdevices. This process is described in a co-pending US Patent Application No. 12/018319, entitled "Microdevice Arrays Formed by Magnetic Assembly," filed on even date herewith. The suitability of any particular external field generator is dependent upon the specific application, particularly the coding space and the selection

criterion. In a preferred embodiment the magnetic field generator consists of a set of nested electromagnetic coils (e.g. Helmholtz coils) that direct magnetic fields along multiple axes (e.g. x,y,z).

[00103] In a preferred embodiment, the magnetic field generators include individual nested sets of electromagnetic coils, similar to Helmholtz coils but wherein the individual coils that would comprise a Helmholtz coil can be independently regulated. In a further preferred embodiment the coils contain magnetic cores such as iron or ferrite. In another preferred embodiment the magnetic field generating system contains a DC power supply capable of producing outputs of either positive or negative polarity. In another preferred embodiment the magnetic field generating system contains an AC power supply or a frequency generator coupled with an amplifier capable of driving the electromagnetic coil. In a further preferred embodiment the magnetic field generating system contains an AC power supply suitable for generating a demagnetizing pulse.

[00104] In a preferred embodiment the magnetic field generator is controllable such that sequences of magnetic field changes can be executed in a programmed manner (for example by means of a set of electromagnetic coils powered by digitally controllable power supplies).

Force Generator for Removing Non-bound Microdevices

[00105] As shown in Figure 1, magnetic discrimination can be used to separate microdevices into a bound and a non-bound state. Non-bound microdevices are microdevices that do not remain arrayed upon application of a lifting force.

[00106] Because of the distance dependence of magnetic interactions the force required to lift the microdevices is much greater than the force required to maintain them in a lifted state. Consequently, once non-bound microdevices have been lifted from the surface the magnetic fields (e.g. z-axis field) holding them up can be decreased weakening the strength of the magnetic force holding the non-bound microdevices to the sorting chip surface. Once the z-axis field has been decreased a larger magnetic field bias can be introduced along any axis to draw the non-bound microdevices into a collection area. Fluidic force is advantageous and can be used alone or in combination with a magnetic field gradient – at low z-axis fields (e.g. after that field has been reduced) microdevices that are in their upright form are easily dislodged – even the addition of a drop of alcohol to an aqueous solution on the sorting chip surface generates sufficient turbulence to dislodge non-bound microdevices. Laboratory

micropipettors are particularly effective at removing non-bound microdevices as demonstrated in the results shown in Figure 23.

[00107] Preferred embodiments include those using fluidic force either alone or in combination with a magnetic force generator. Additional preferred embodiments include the use of vibratory forces, fluidic force, acoustic force, dielectrophoretic force, etc. as described in US Patent Application 20020137059. These forces can be used alone or in combinations and these combinations can include a magnetic force generator.

Synthesis

[00108] Magnetic sorting and arraying offer significant advantages in the area of library synthesis and screening. Particle-based libraries can be produced by synthesizing compounds directly onto microdevices. Solid phase synthesis methods are widely used and microdevice surface chemistry can be constructed so as to be compatible with existing solid phase synthesis protocols. Embodiments described herein can be used to track microdevices in a random split and mix approach. In a preferred embodiment one can assign specific synthesis steps to a microdevice, such that a compound to be synthesized can be associated with a particular magnetic code or portion of a magnetic code. In a preferred embodiment the microdevices comprise an optical code. This code can be the magnetic code or it can be an independent nonmagnetic layer. A sorting process results in all microdevices being displayed in an arrayed format. This feature in concert with an optically detectable code can be utilized to monitor the microdevices during a sorting process. In a preferred embodiment an optical quality check can be performed to verify arraying accuracy. In another preferred embodiment a synthesis process can be carried out using optically detectable protecting groups (e.g. fluorescently labeled) or an optically detectable test of coupling efficiency can be carried out such that at any step in that synthesis process coupling efficiencies can be estimated (e.g. as discussed in "The one-bead-one-compound combinatorial method" by Lam et al. Chem. Rev. 97:411-448 (1997)). In another preferred embodiment each microdevice has a unique optical code, such that coupling efficiency for compounds on each microdevice can be determined at a step in the synthesis process. In another preferred embodiment microdevices contain an independent magnetic group code allowing a predetermined subset of codes to be collected.

[00109] Embodiments of the present invention provide a substantial improvement over existing methods in the manufacture and screening of libraries. The ability to rapidly sort and display microdevices allows large compound specific particle libraries to be produced and

researched. A compound specific particle library is one in which the compounds in the library are assigned to individual particles prior to a synthetic step. Most particle-based libraries are random involving split-and-mix type procedures (reviewed in Lam et al. 1997). However, the specific compounds contained in split-and-mix libraries can not be determined unless the libraries generated are "fully combinatorial", meaning that the library contains all possible combinations of building blocks (e.g. amino acids, nucleotides, etc). Since such combinatorial libraries are generally extremely large, in practice the actual composition of the random library is not known. By arraying before and/or after each split and mix step and keeping track of the identities of the microdevices through identification of their coding patterns the precise composition of the random library can be determined. In addition such information allows the identity of the compound on each encoded microdevice to be known facilitating the screening process. By contrast a compound specific library allows the library to contain any desired subset of compounds. Such compound specific libraries are produced by a directed sorting process in which at each step in the synthesis process particles of known identity are directed to a particular reaction chamber. Libraries produced using NEXUS Biosystems IRORI solid phase combinatorial chemistry synthesis systems are a widely used commercially available example of compound specific libraries produced by a directed sorting process. Such commercial libraries generally contain less than 10,000 compounds.

[00110] As an example, consider a library comprising 10-residue peptides composed of the 20 naturally occurring amino acids. There are over 10^{13} different possible peptides (20^{10}) in the library. A random particle-based library would need to contain many more particles than possible compounds in order to have a library that contained all possible peptides. Alternatively, the random library could contain only a random subset of the 10-residue peptides. By contrast the compound specific particle library can contain any desired predetermined subset of 10-residue peptides since each magnetically coded particle can be assigned to a specific peptide. For example, a 10-residue peptide library that contains all the possible peptides in the human genome could be used to screen for a physiologically relevant process, e.g., enzymatic specificity, binding of a soluble receptor, antibody binding, kinase activity, etc. There are $\sim 10^7$ such peptides encoded by the human genome, but a random library would need to contain 10^{13} compounds to include them. Ignoring the large volume needed to screen such a random library there would still be considerable interference during screening from the 10^{13} non-physiologically relevant peptides. By contrast the compound specific library can be constructed so as to only contain the 10^7 desired peptides.

[00111] An additional advantage of arraying the microdevices at each step in the synthetic process is that in addition to the identity of the microdevice a measure of the coupling efficiency of that synthetic step on each individual microdevice can be determined through the use of nondestructive assays (e.g. colorimetric or fluorogenic). For example in the case of peptide synthesis, there are established assays that can be used to determine the completion of coupling at the level of individual beads (Lam et al. 1997). However, in a random bead library since it is not feasible using current bead encoding technologies to routinely decode the entire library this information is of limited utility; determining that the efficiency of a coupling step was greater than 95% on 95% of the beads does not determine the level or purity or the composition of the major side products on any individual bead. Such particle specific information is of great importance when interpreting results obtained from researching (e.g. screening for function or activity) the library. For example, a group of microdevices containing very different main products could contain significant amounts of similar side products due to incomplete reactions occurring at various steps in the synthesis. By tracking this information at every step in the synthesis the distribution of side products can be recorded. The ability of the microdevice to contain sensors or other types of MEMS devices offers additional advantages in researching the library by allowing the microdevices to serve as both the substrate for synthesis as well as the analysis device.

[00112] The following example serves to illustrate the utility of these embodiments. Synthesis of a library of 100,000 compounds is carried out using 10 million microdevices. The microdevices contain a chemically reactive site (e.g. a well comprising a chemically reactive surface displaying an appropriate linker). The magnetic coding space used for sorting the library has greater than one million representations. The magnetic coding space is divided such that there at least 100,000 magnetic sorting codes and 10 group codes. A group code is simply another way of dividing a magnetic coding space such that specific sets of microdevices can be sorted as a group. In this particular example the group codes are assigned uniformly to each sorting code such that for the 100 copies of each sorting code in the library, exactly 10 contain any particular group code. Therefore, each microdevice has a unique optical code, a magnetic sorting code shared by 100 other microdevices, and a group code shared by one million other microdevices. Prior to the start of the synthesis process each compound to be synthesized is assigned to a magnetic sorting code. This assignment will determine the reaction chambers each microdevice will be placed into at each step in the synthesis process. Microdevices are placed on a sorting chip and sorted into eluted groups

(e.g. see Figure 13) and the groups placed into the appropriate reaction vessels for the first synthesis step. After an appropriate reaction time the microdevices are washed and arrayed on a sorting chip and placed in an optical reader (e.g. microscope or fluorescence scanner) and their optical codes are determined and recorded along with the results of the fluorogenic or colorimetric assay used to monitor the reaction. Another sorting process is carried out and the next synthesis step is started. This process is repeated until the synthesis of the library is complete (e.g. a library of 10-residue peptides would require 10 such cycles). At the end of the synthesis process the percent yield and the distribution of impurities for each optical code has been determined. Following synthesis the microdevices are sorted based on their group code to generate 10 groups. Each group contains 10 copies of each type of magnetic code. This process generates 10 copies of the library with each copy of the library containing 10 copies of each compound wherein the purity of the compound synthesized on each microdevice has been characterized.

[00113] In libraries where each microdevice contains a unique optical code, each compound can be represented by multiple optical codes (e.g. 10). This allows errors to be identified during a synthesis process and ignored or accounted for during the analysis of the library. For example the optical codes on the microdevices can be monitored at the end of every arraying step in the sorting process, consequently if during step 8 in a 15 step process the microdevice containing optical code 2341 was misarrayed, the composition of the compound on that microdevice can be known and therefore any analysis results for that microdevice will not adversely affect the analysis of other microdevices that share the same magnetic sorting code and were supposed to contain the same compound.

[00114] The use of group codes provides a significant advantage over other methods of making multiple copies of a library since it overcomes the poisson distribution problem that occurs when randomly dividing large collections of objects into groups.

[00115] In addition to enabling compound specific library synthesis, embodiments of the current invention also provide a substantial improvement in the manufacture and screening of random libraries. All of the advantages that apply to compound-specific libraries that arise from the ability to display particles in an oriented form also apply to random libraries.

[00116] The ability to synthesize a library of known predetermined composition and large size allows for sequential library synthesis to be carried out to rapidly identify a compound of

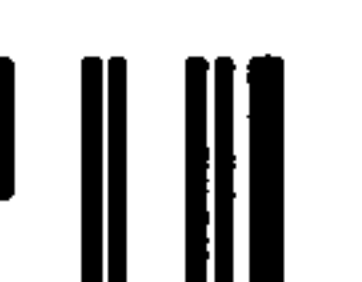
interest. For example, after screening a first library a new second library can be designed based on the results obtained by studying the first library. The process can be continued until the desired screening result is obtained and a synthetic compound with the desired properties is identified. Such synthetic compounds include inhibitory molecules, drugs, binding molecules, catalysts, etc. Any compound that can be synthesized on a solid support falls within the scope of this invention.

Target Isolation

[00117] Embodiments described herein can be used to isolate any item of interest that can be attached to a microdevice and distinguished by some optical procedure (either directly or indirectly). A preferred example is rare cell isolation. A mixture of cells can be attached to microdevices such that a plurality of microdevices contains a single cell. After arraying microdevices containing the cells of interest can be identified by optical methods (e.g. fluorescence) and those microdevices isolated. Cells can be targeted with an optical marker at any step of this process prior to the optical detection step. Isolated cells can then be used for further analysis (e.g. gene expression, SNP analysis, proteomic profiling, etc).

[00118] It should be apparent to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. Moreover, in interpreting the disclosure, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms “comprises” and “comprising” should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating that the referenced elements, components, or steps could be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced. Where the specification claims refers to at least one of something selected from the group consisting of A, B, C and N, the text should be interpreted as requiring only one element from the group, not A plus N, or B plus N, etc.

Table 1

		A		B
1		1-16, 21-26, 36-41		17-20, 27-35, 42-56
2		1-13, 17-19, 21-23, 27-29, 36-38, 42-44		14-16, 20, 24-26, 30-35, 39-41, 45-56
3		1-11, 14, 15, 17, 19-21, 24, 25, 27, 28, 30, 36, 39, 40, 42, 43, 45		12, 13, 16, 18, 22, 23, 26, 29, 31-35, 37, 38, 41, 44, 46-56
4		1-10, 12, 14, 16, 17, 18, 20, 22, 24, 26, 27, 29, 30, 37, 39, 41, 42, 44, 45		11, 13, 15, 19, 21, 23, 25, 28, 31, 32, 33, 34, 35, 36, 38, 40, 43, 46, 47, 48-56
5		1-10, 13, 15, 16, 18, 19, 20, 23, 25, 26, 28-30, 38, 40, 41, 43-45		11, 12, 14, 17, 21, 22, 24, 27, 31-37, 39, 42, 46-56
6		1-7, 11-19, 21-23, 31-33, 36-38, 46-48		8-10, 20, 24-30, 34, 35, 39-45, 49-56
7		1-5, 8, 9, 11-17, 19, 20, 21, 24, 25, 31, 32, 34, 36, 39, 40, 46, 47, 49		6, 7, 10, 18, 22, 23, 26-30, 33, 35, 37, 38, 41-45, 48, 50-56
8		1-4, 6, 8, 10-18, 20, 22, 24, 26, 31, 33, 34, 37, 39, 41, 46, 48, 49		5, 7, 9, 19, 21, 23, 25, 27-30, 32, 35, 36, 38, 40, 42-45, 47, 50-56
9		1-4, 7, 9-16, 18-20, 23, 25, 26, 32-34, 38, 40, 41, 47-49		5, 6, 8, 17, 21, 22, 24, 27-31, 35-37, 39, 42-46, 50-56
10		1, 2, 5-9, 11-15, 17-21, 27, 28, 31, 32, 35, 36, 42, 43, 46, 47, 50		3, 4, 10, 16, 22-26, 29, 30, 33, 34, 37-41, 44, 45, 48, 49, 51-56
11		1, 3, 5-8, 10-14, 16-20, 22, 27, 29, 31, 33, 35, 37, 42, 44, 46, 48, 50		2, 4, 9, 15, 21, 23-26, 28, 30, 32, 34, 36, 38-41, 43, 35, 47, 49, 51-56
12		1, 4-7, 9-13, 15-20, 23, 28, 29, 32, 33, 35, 38, 43, 44, 47, 48, 50		2, 3, 8, 14, 21, 22, 24-27, 30, 31, 34, 36, 37, 39-42, 45, 46, 49, 51-56

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13		2, 3, 5, 6, 8-12, 14-20, 24, 27, 30, 31, 34, 35, 39, 42, 45, 46, 49, 50		1, 4, 7, 13, 21-23, 25, 26, 28, 29, 32, 33, 36-38, 40, 41, 43, 44, 47, 48, 51- 56
14		2, 4, 5, 7-11, 13- 20, 25, 28, 30, 32, 34, 35, 40, 43, 45, 47, 49, 50		1, 3, 6, 12, 21-24, 26, 27, 29, 31, 33, 36-39, 41, 42, 44, 46, 48, 51-56
15		3, 4, 6-10, 12-20, 26, 29, 30, 33-35, 41, 44, 45, 48-50		1, 2, 5, 11, 21-25, 27, 28, 31, 32, 36- 40, 42, 43, 46, 47, 51-56
16		1-7, 11-13, 21-29, 31-33, 36-38, 51- 53		8-10, 14-20, 30, 34, 35, 39-50, 54- 56
17		1-5, 8, 9, 11, 14, 15, 21-28, 30-32, 34, 36, 39, 40, 51, 52, 54		6, 7, 10, 12, 13, 16-20, 29, 33, 35, 37, 38, 41-47, 48- 50, 53, 55, 56
18		1-4, 6, 8, 10, 12, 14, 16, 18, 21-27, 30, 31, 33, 34, 37, 39, 41, 51, 53, 54		5, 7, 9, 11, 13, 15, 17, 19, 20, 28, 29, 32, 35, 36, 38, 40, 42-50, 52, 55, 56
19		1-4, 7, 9, 10, 13, 15, 16, 21-26, 28- 30, 32-34, 38, 40, 41, 52-54		5, 6, 8, 11, 12, 14, 17-20, 27, 31, 35- 37, 39, 42-51, 55, 56
20		1, 2, 5-9, 11, 17, 19, 21-25, 27-32, 35, 36, 42, 43, 51, 52, 55		3, 4, 10, 12-16, 18, 20, 26, 33, 34, 37-41, 44-50, 53, 54, 56
21		1, 3, 5-8, 10, 12, 17, 18, 21-24, 26- 31, 33, 35, 37, 42, 44, 51, 53, 55		2, 4, 9, 11, 13-16, 19, 20, 25, 32, 34, 36, 38-41, 43, 45- 50, 52, 54, 56
22		1, 4-7, 9, 10, 13, 18, 19, 21-23, 25- 30, 32, 33, 35, 38, 43, 44, 52, 53, 55		2, 3, 8, 11, 12, 14- 17, 20, 24, 31, 34, 36, 37, 39-42, 45- 51, 54, 56
23		2, 3, 5, 6, 8-10, 14, 17, 20-22, 24- 31, 34, 35, 39, 42, 45, 51, 54, 55		1, 4, 7, 11-13, 15, 16, 18, 19, 23, 32, 33, 36-38, 40, 41, 43, 44, 46-50, 52, 53, 56
24		2, 4, 5, 7-10, 15, 19-21, 23-30, 32,		1, 3, 6, 11-14, 16- 18, 22, 31, 33, 36-

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		34, 35, 40, 43, 45, 52, 54, 55		39, 41, 42, 44, 46-51, 53, 56
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26		1, 2, 5, 11-15, 17, 19, 21-25, 27, 28, 31-36, 46-47, 51, 52, 56		3, 4, 6, 7-10, 16, 18, 20, 26, 29, 30, 37-45, 48-50, 53- 55
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28		1, 4, 7, 11-13, 15, 16, 18, 19, 21-23, 25, 26, 28, 29, 31-35, 38, 47, 48, 52, 53, 56		2, 3, 5, 6, 8-10, 14, 17, 20, 24, 27, 30, 36, 37, 39-46, 49-51, 54, 55
29		2, 3, 8, 11, 12, 14- 17, 20-22, 24-27, 30-35, 39, 46, 49, 51, 54, 56		1, 4-7, 9, 10, 13, 18, 19, 23, 28, 29, 36-38, 40-45, 47, 48, 50, 52, 53, 55
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31		3, 4, 10, 12-16, 18, 20, 22-26, 29- 35, 41, 48, 49, 53, 54, 56		1, 2, 5-9, 11, 17, 19, 21, 27, 28, 36- 40, 42-47, 50-52, 55
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35		8-10, 14-20, 24- 35, 45, 49, 50, 54- 56		1-7, 11-13, 21-23, 36-44, 46-48, 51- 53

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AMENDED CLAIMS**received by the International Bureau on 04 August 2008 (04.08.2008)**

What is claimed is:

1. A method of sorting microdevices, comprising:
 - providing microdevices having magnetically distinguishable device codes;
 - providing an array having discrete coded regions comprising magnetic region codes, and that exert magnetic forces;
 - using the magnetic forces to orient the microdevices with respect to the regions as a function of the device and region codes; and
 - applying a removing force to the oriented microdevices under conditions that remove a proper subset of the microdevices from the array as a function of differing orientations of the microdevices.
2. The method of claim 1, wherein the microdevices have a longest linear dimension of 0.1 to 500 μm , inclusive.
3. The method of claim 1, further comprising repeating the steps of using the magnetic force and applying a removing step.
4. The method of claim 1, further comprising utilizing a set of the microdevices that utilize a magnetic coding space that supports at least 10 choices.
5. The method of claim 1, further comprising utilizing a set of the microdevices that utilize a magnetic coding space that supports at least 10^3 choices.
6. The method of claim 1, further comprising utilizing a set of the microdevices that utilize a magnetic coding space that supports at least 10^6 choices.
7. The method of claim 1, further comprising utilizing a set of the microdevices each comprising a magnetic material sized and dimensioned to have an aspect ratio of at least 1.2 and having a predetermined preferential axis of magnetization.
8. The method of claim 1, wherein the step of using the magnetic forces to orient the microdevices comprises causing members of the subset of microdevices to stand up relative to ones of the microdevices outside the subset.
9. A method of sorting, comprising:

using microdevices that have magnetically distinguishable device codes, a
predetermined preferential axis of magnetization, and that utilize a magnetic
coding space that can support at least 10 choices;
using a magnetic force to orient the microdevices with respect to coded regions
having magnetic region codes as a function of the device and the region codes.

10. The method of claim 1, wherein the microdevices have a longest linear dimension of 0.1 to 500 μm , inclusive, and at least some of the microdevices utilize a magnetic coding space that supports at least 10^3 choices.

11. The method of claim 9, wherein at least some of the microdevices utilize a magnetic coding space that supports at least 10^6 choices.

12. A method of sorting:

positioning a set of microdevices having magnetically distinguishable device codes on
an array having coded regions comprising magnetic region codes;
applying a magnetic field to the microdevices in a manner that alters magnetic
interactions of a subset of the microdevices with the array as a function of the
device and region codes; and
selectively removing the subset of microdevices from the array.

13. The method of claim 1, wherein each of the microdevices in the set have a longest linear dimension of 0.1 to 500 μm , inclusive, and a chemically active site.

14. The method of claim 13, further comprising repeating the steps of applying the magnetic force and selectively removing at least five times.

15. The method of claim 13, further comprising utilizing a set of the microdevices that utilize a plurality of magnetic coding regions that utilize a coding space that supports at least 10 choices.

16. A method of performing combinatorial chemistry, comprising:

providing a plurality of magnetically orientable microdevices, each of which includes
a chemically reactive site, and each of which includes a magnetic code;
using magnetic orientation of the microdevices to divide the microdevices into at least
first and second sets;

performing different reactions at the reactive sites of the microdevices in the first and second sets, and then recombining at least portions of the first and second sets of microdevices;
using magnetic orientation of the microdevices to divide the microdevices from the recombined first and second sets into at least third and fourth sets; and
performing different reactions at the reactive sites of the microdevices in the third and fourth sets, and then recombining at least portions of the third and fourth sets of microdevices.

17. The method of claim 16, further comprising at least partially sorting at least some of the microdevices as a function of the orientation of such microdevices on an array.

18. The method of claim 16, further comprising using the step of sorting to facilitate dividing the microdevices from the recombined first and second sets into the at least third and fourth sets.

19. The method of claim 17, wherein at least some of the codes support at least 10^3 distinct choices.

20. The method of claim 16, wherein at least some of the codes support at least 10^6 distinct choices.

21. A method of displaying, comprising:

providing a set of microdevices, different ones of which include different magnetically distinguishable device codes;
providing an array having a first and second arraying sites comprising magnetic site codes that complement different ones of the device codes,
adding the microdevices to the array; and
applying an external magnetic field to the array such that distinct subsets of the microdevices select to the first and second sites, respectively, as a function of the device and site codes.

22. The method of claim 21 further comprising at least an additional 8 arraying sites that complement different magnetic codes from the first and second arraying sites.

23. A library comprising first, second and third microdevices, each of which has a mutually distinct magnetically distinguishable device code, and a region with a mutually distinct chemical moiety, and further comprising an array of arrayed sites wherein at least one site comprises a magnetic site code that complements the device code of the first microdevice.
24. The library of claim 23, wherein each of the mutually distinct chemical moieties are polymers.
25. The library of claim 23, wherein each of the mutually distinct chemical moieties are peptides or nucleic acids.
26. A chemical entity researched through use of the library of claim 23.

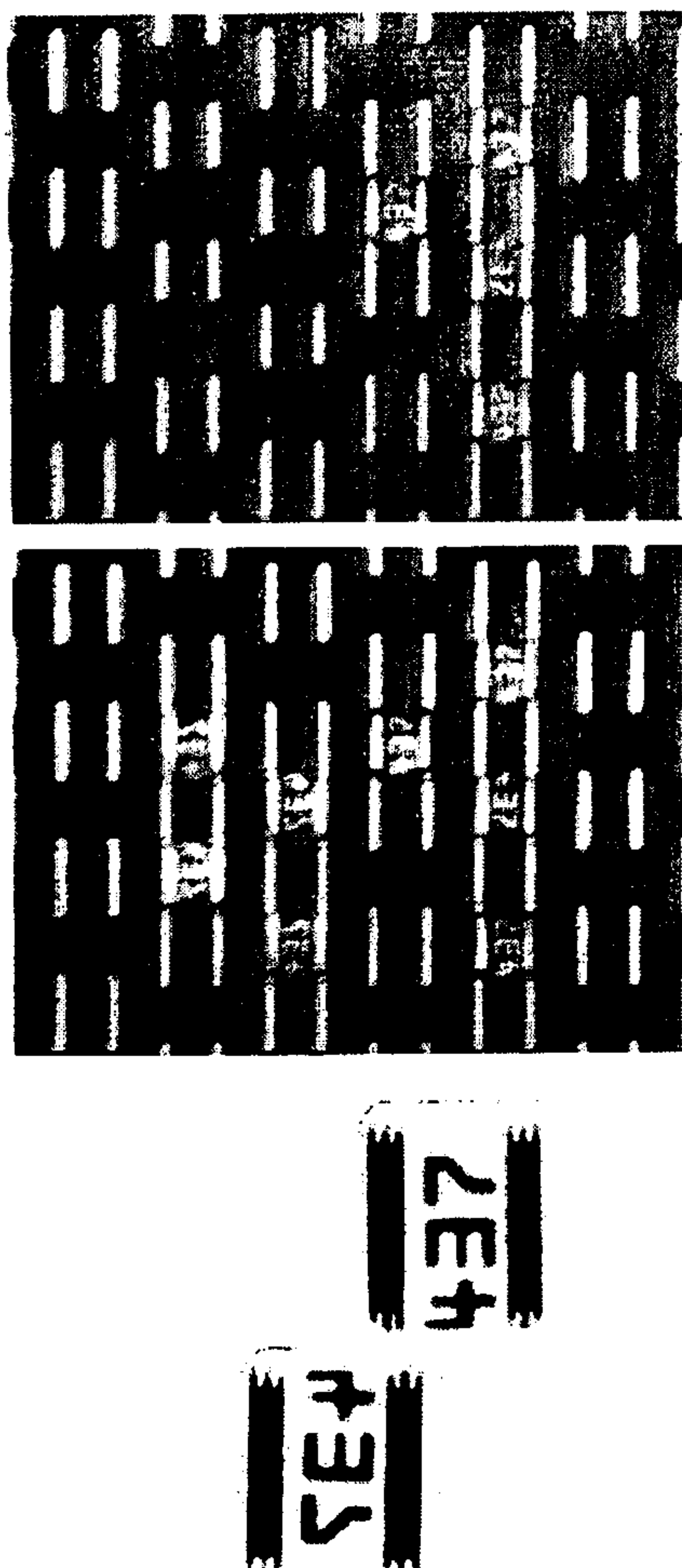
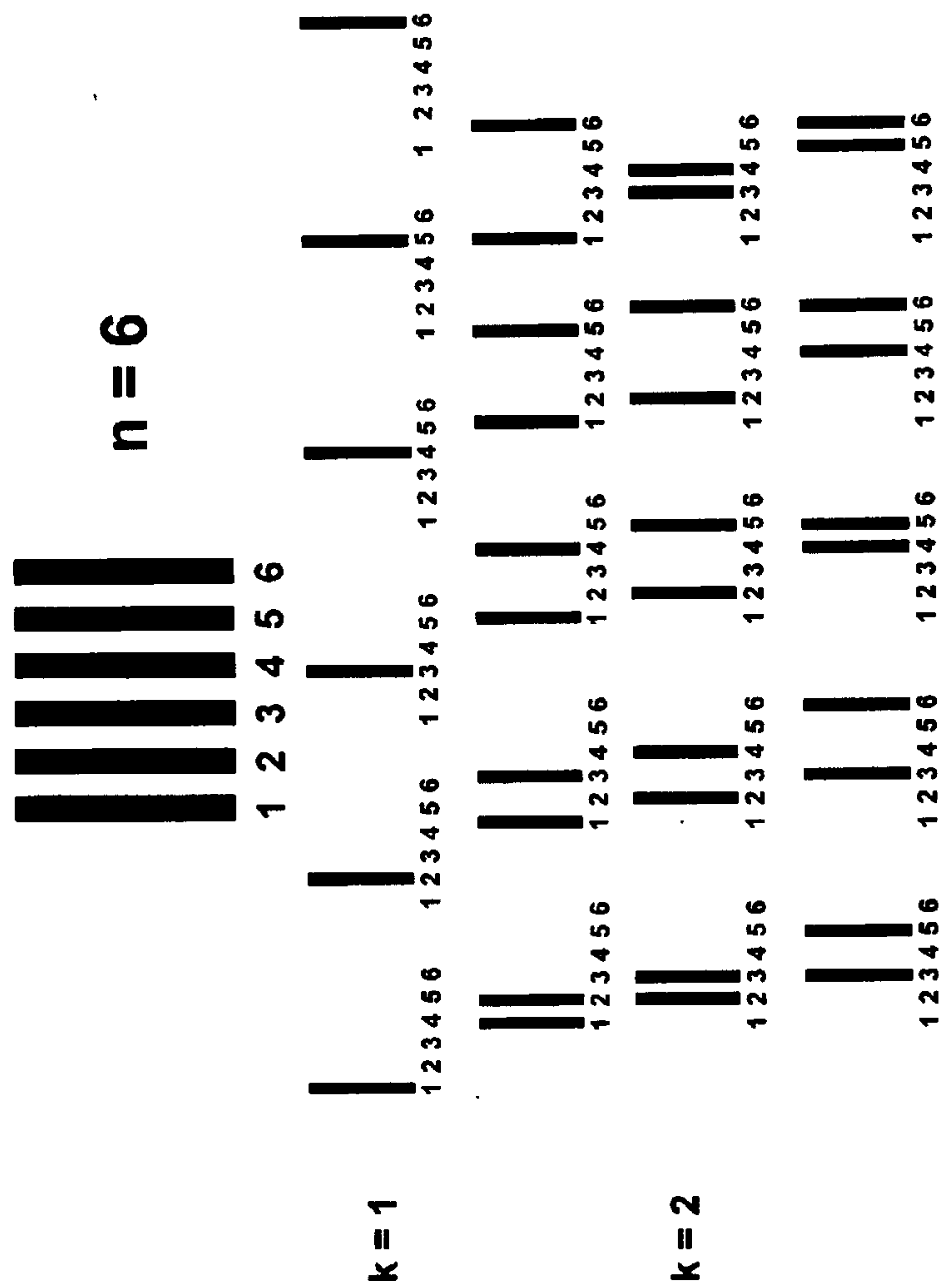
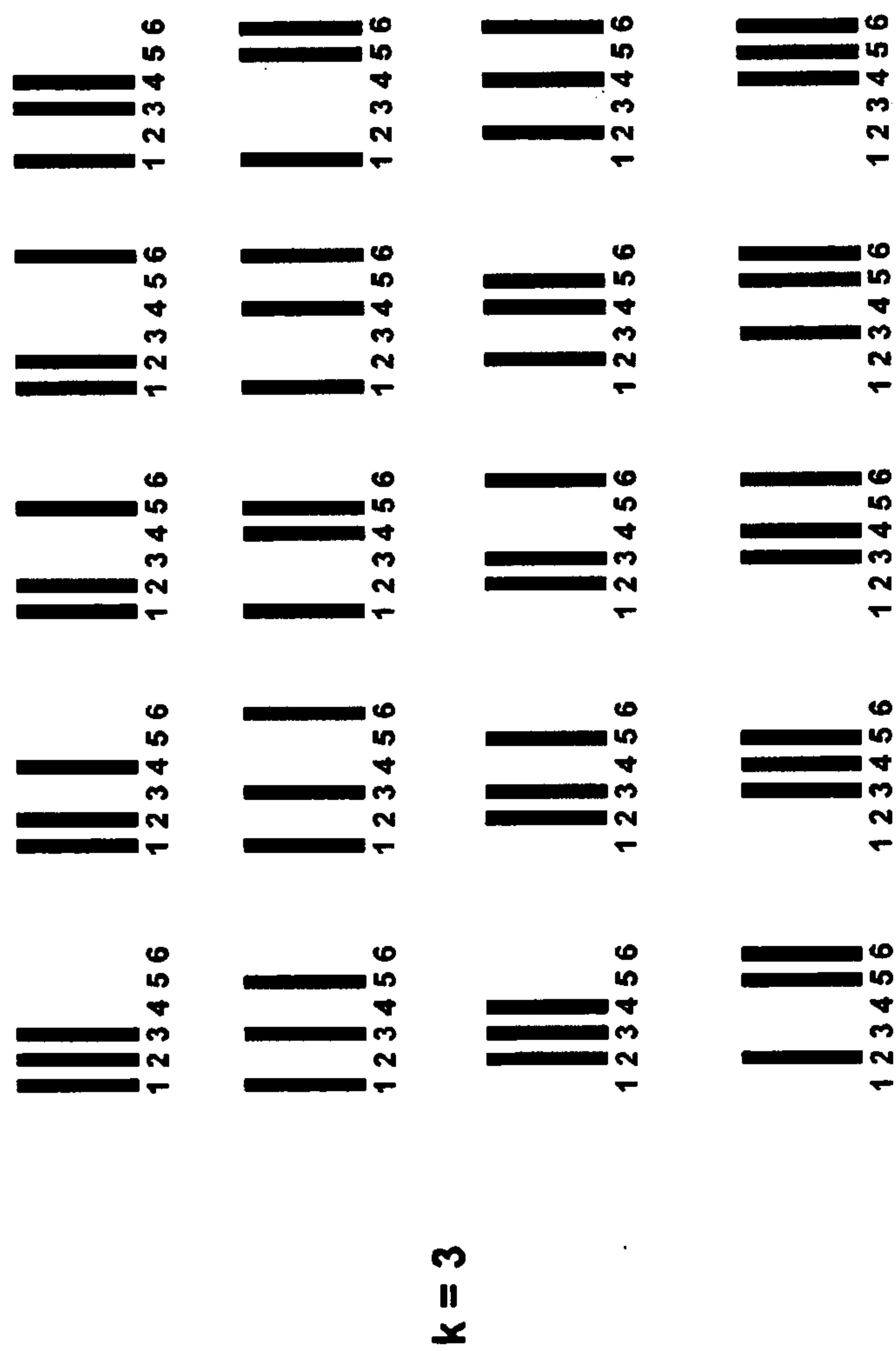
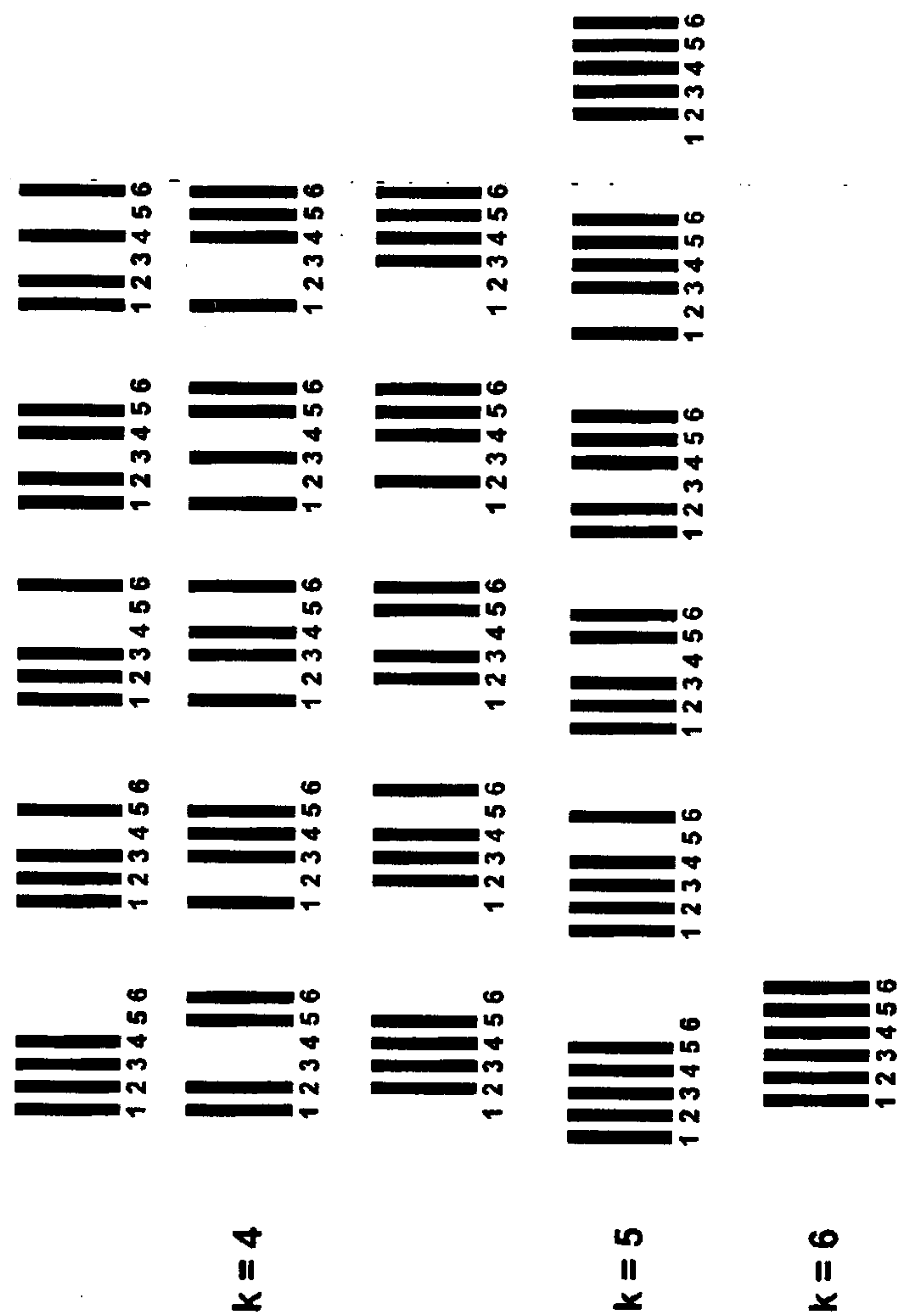


Figure 1

**Figure 2A**

**Figure 2B**

**Figure 2C**

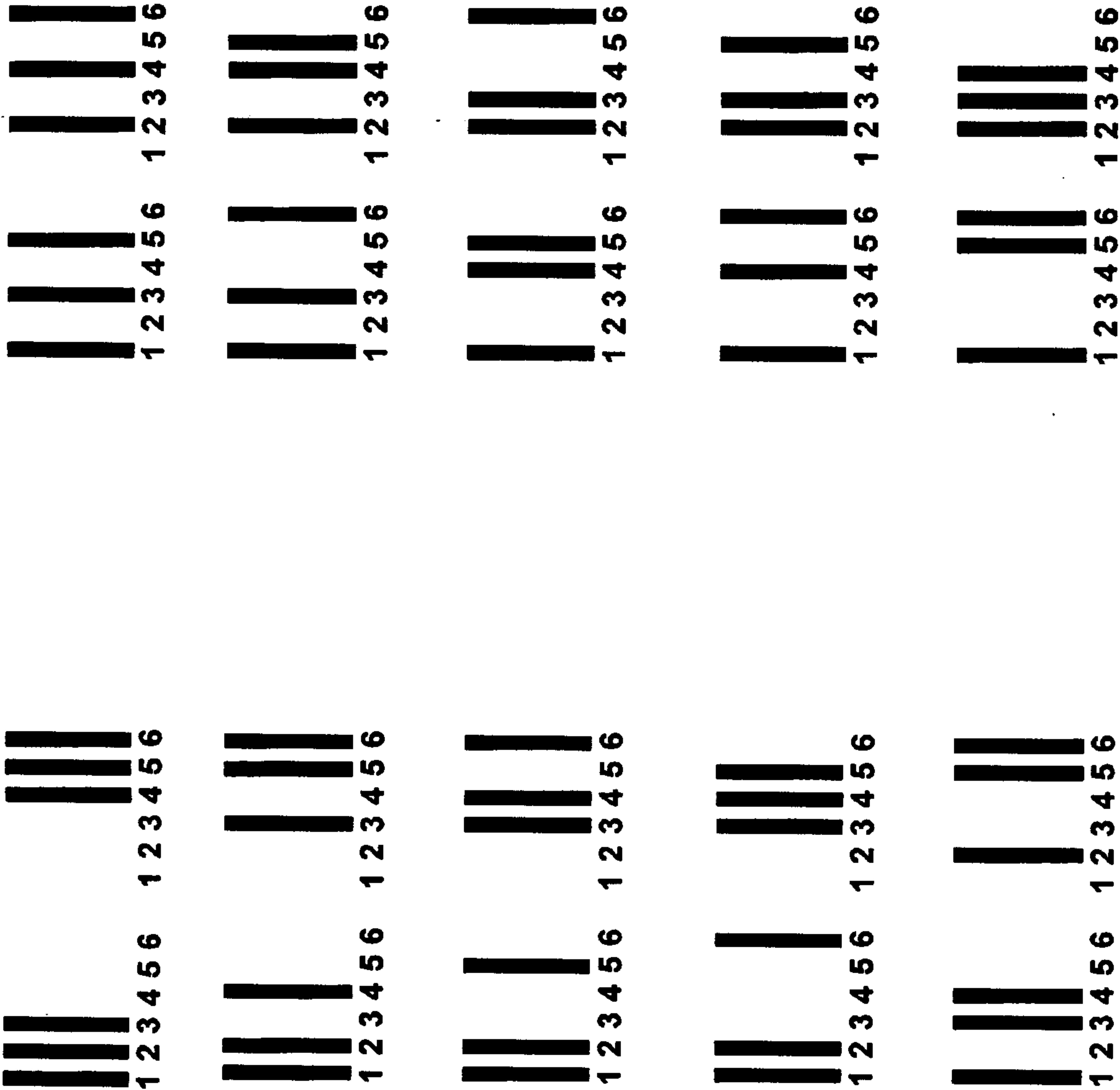


Figure 3

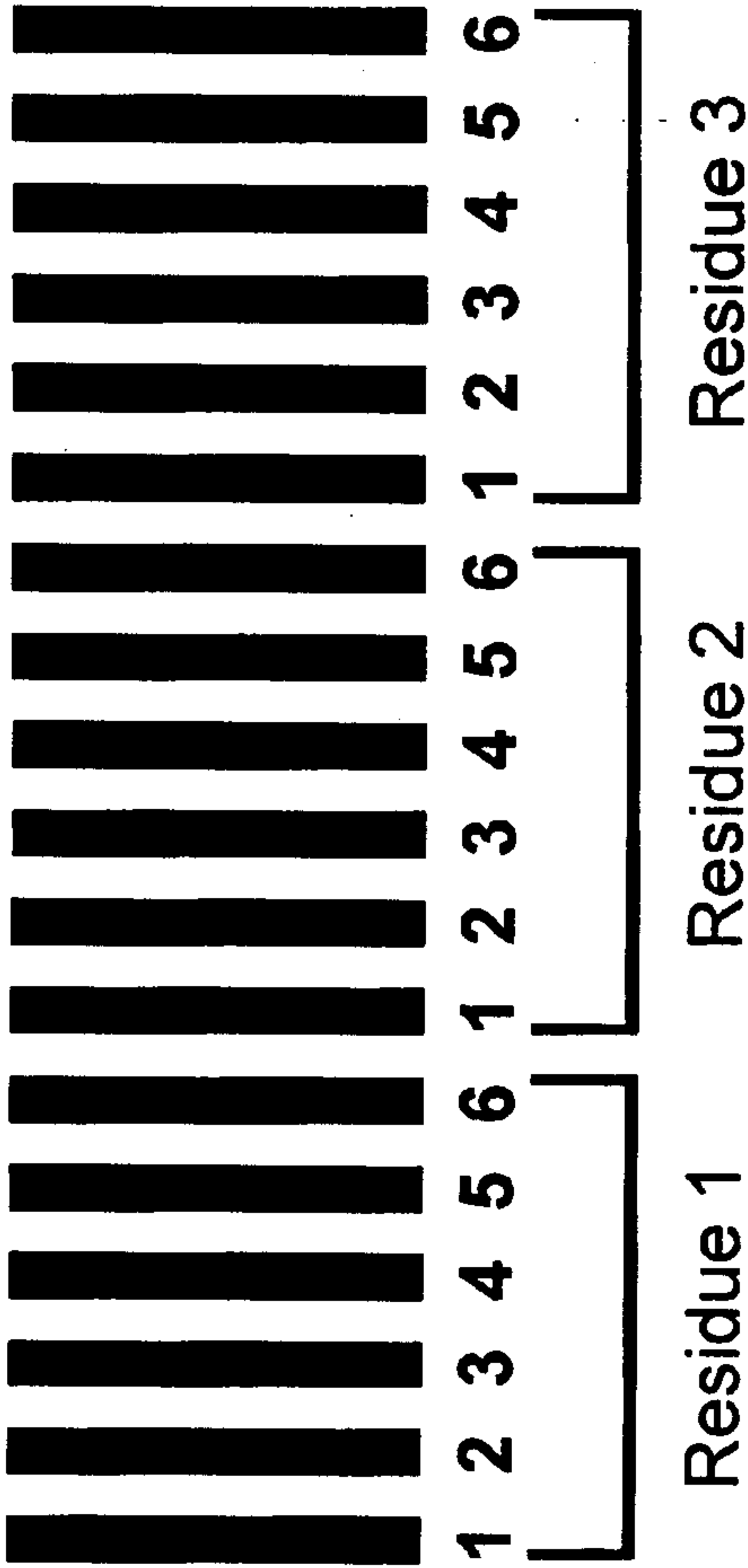
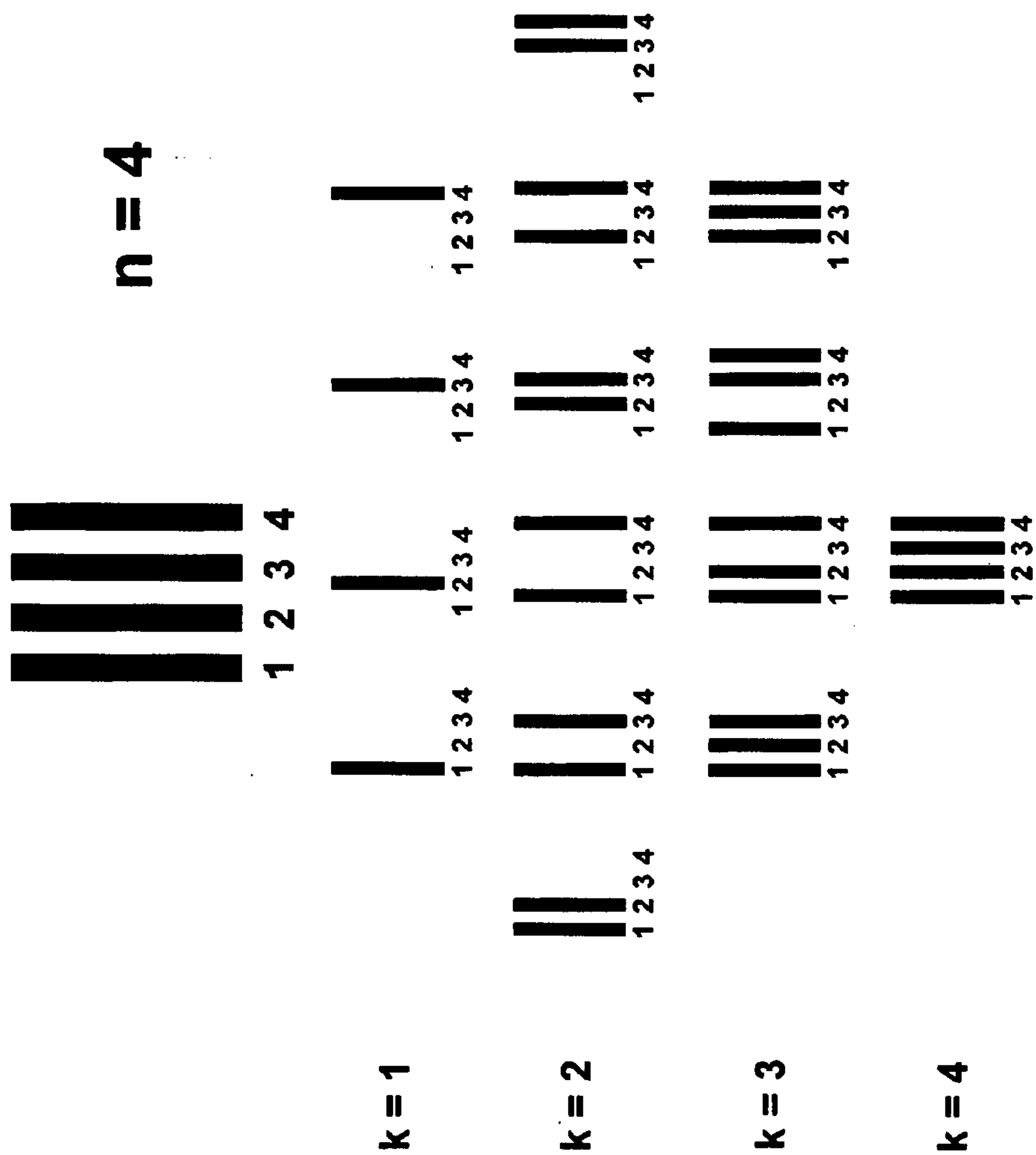


Figure 4

**Figure 5**

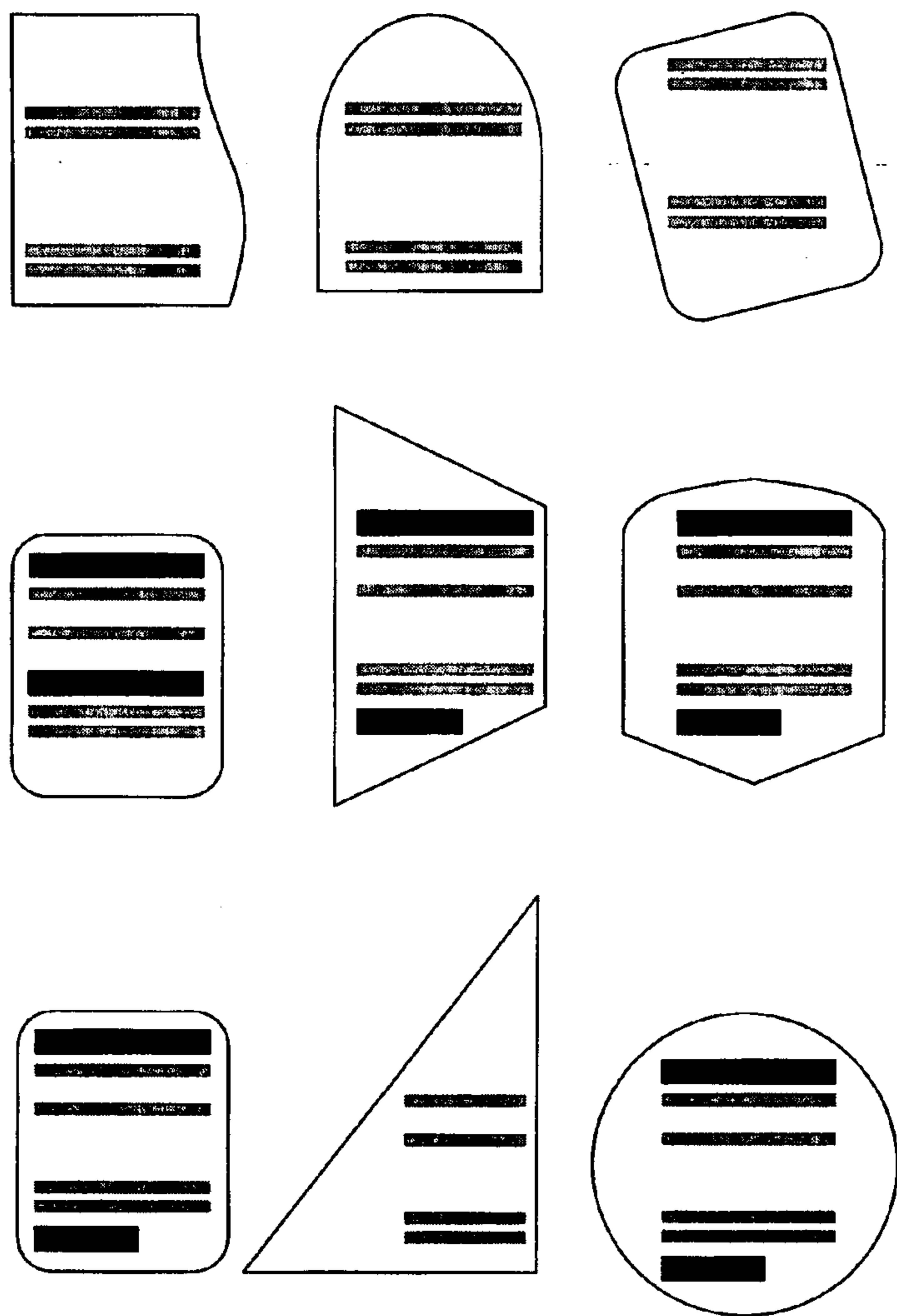
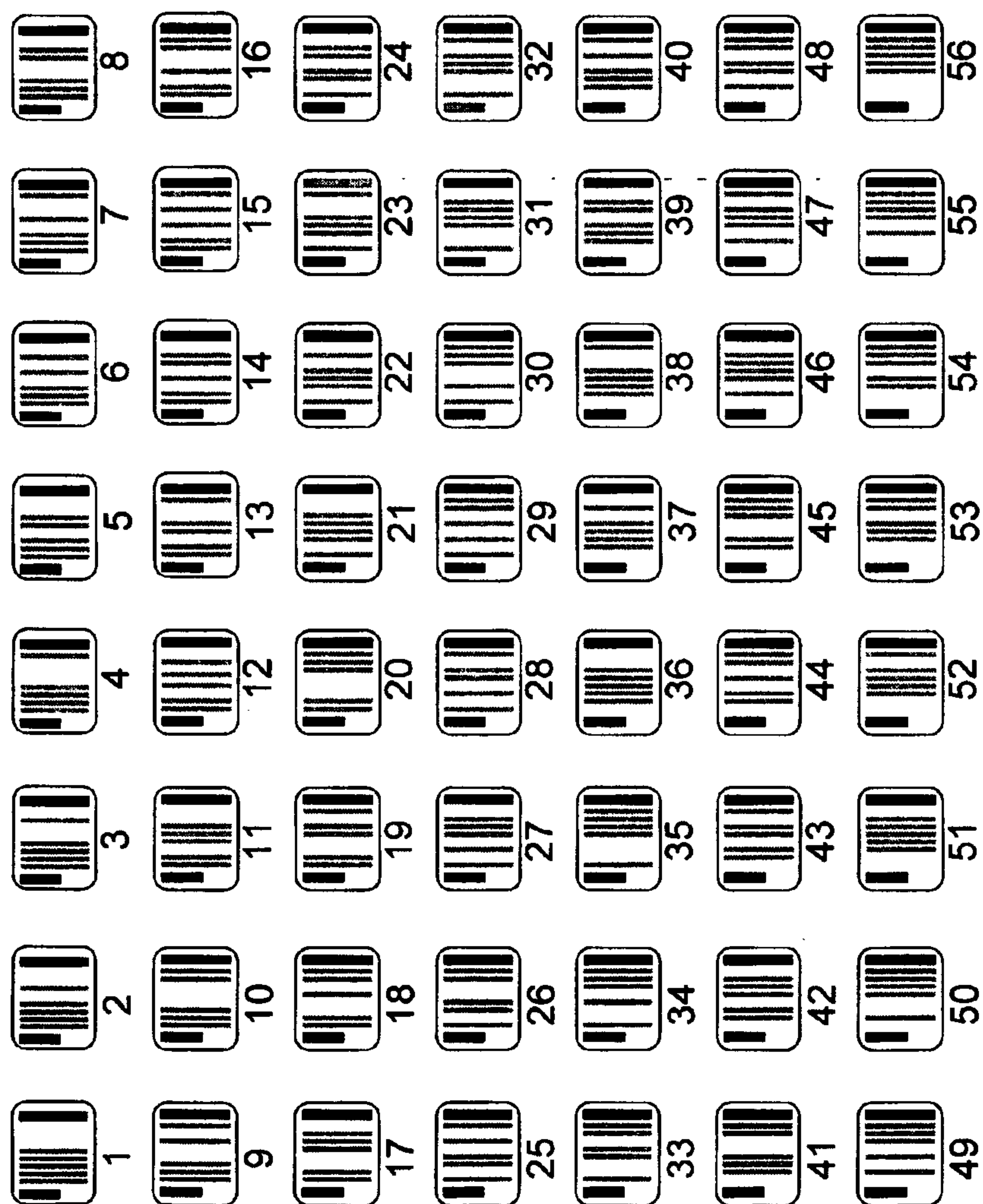
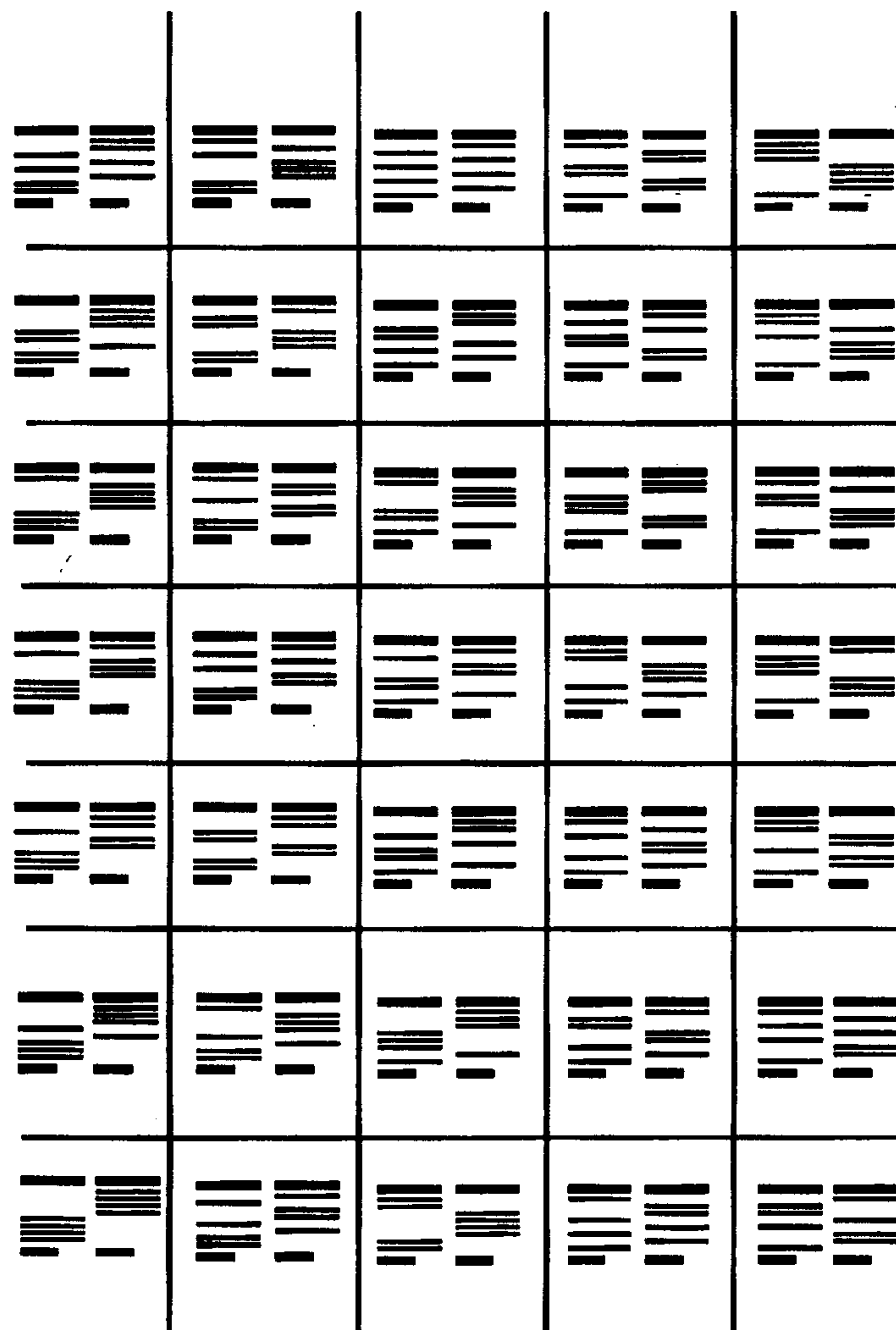
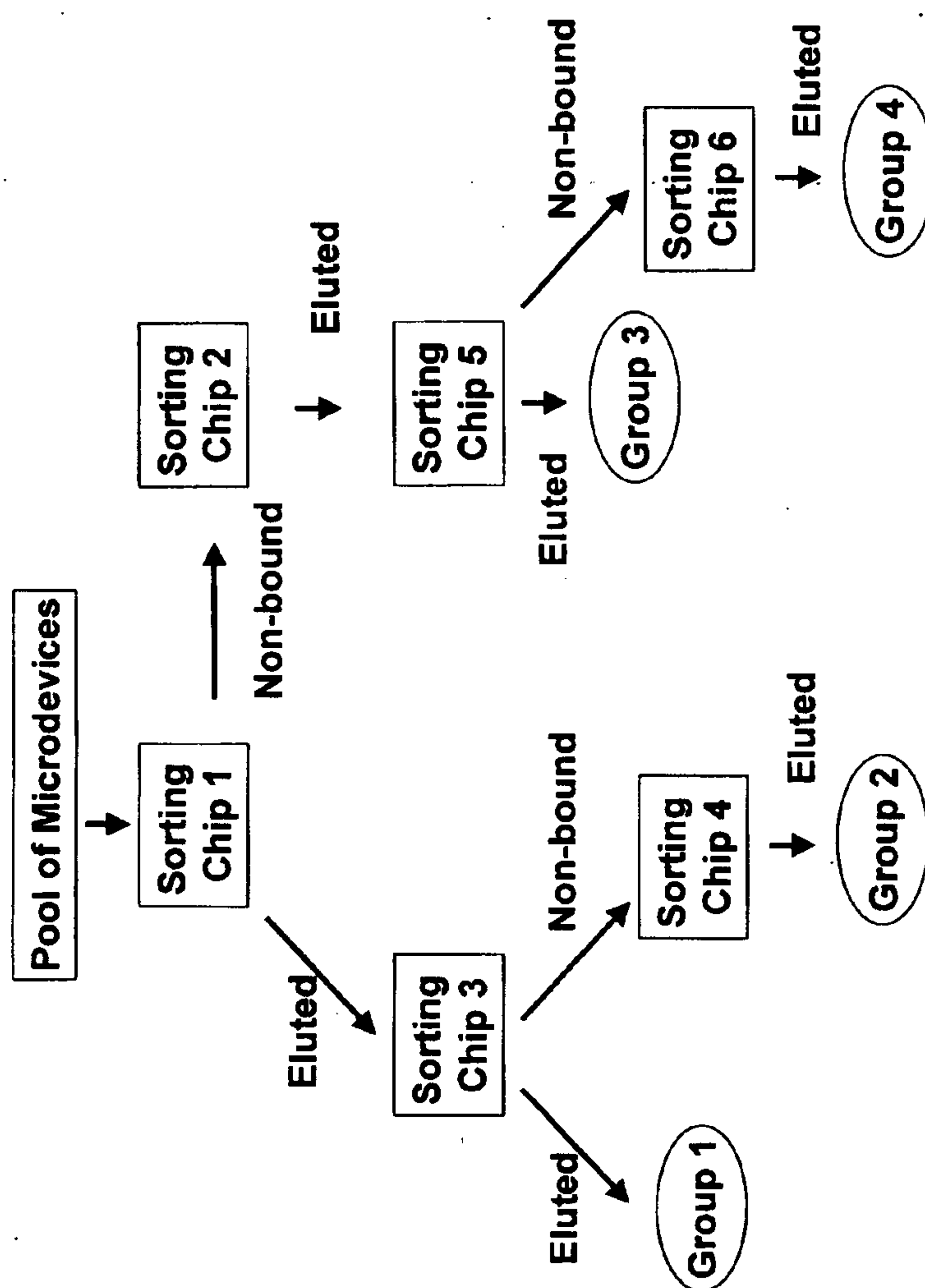
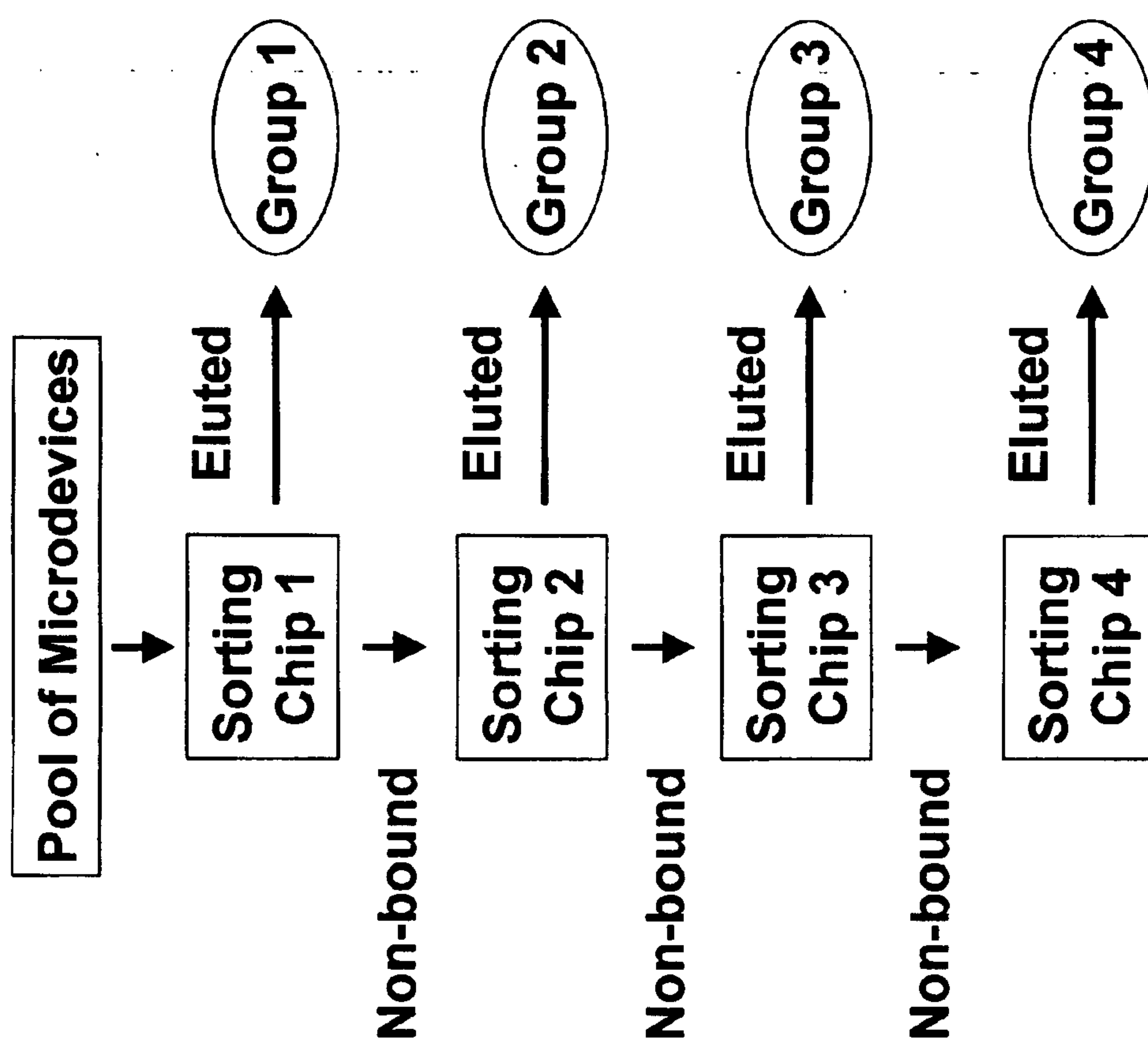


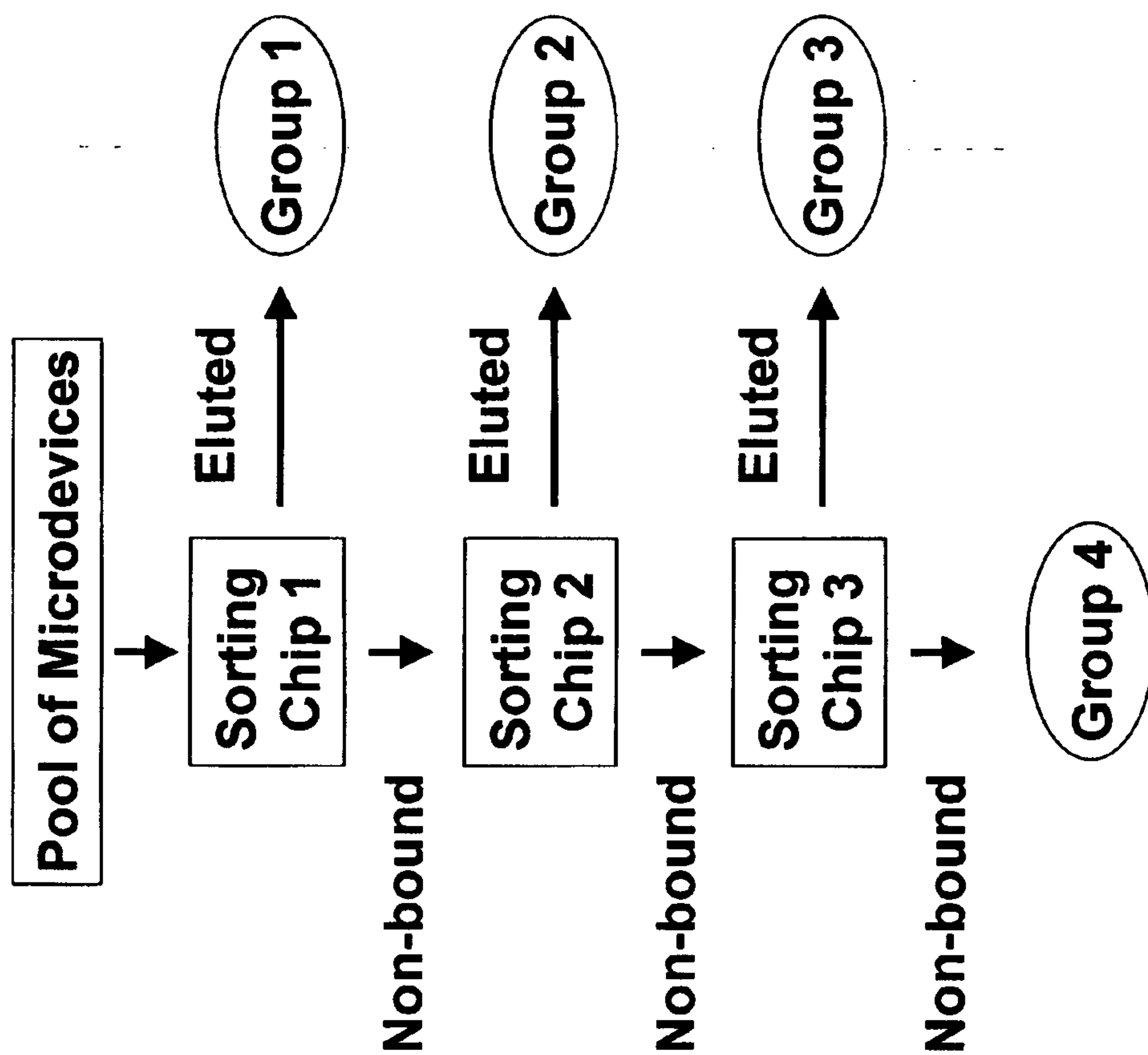
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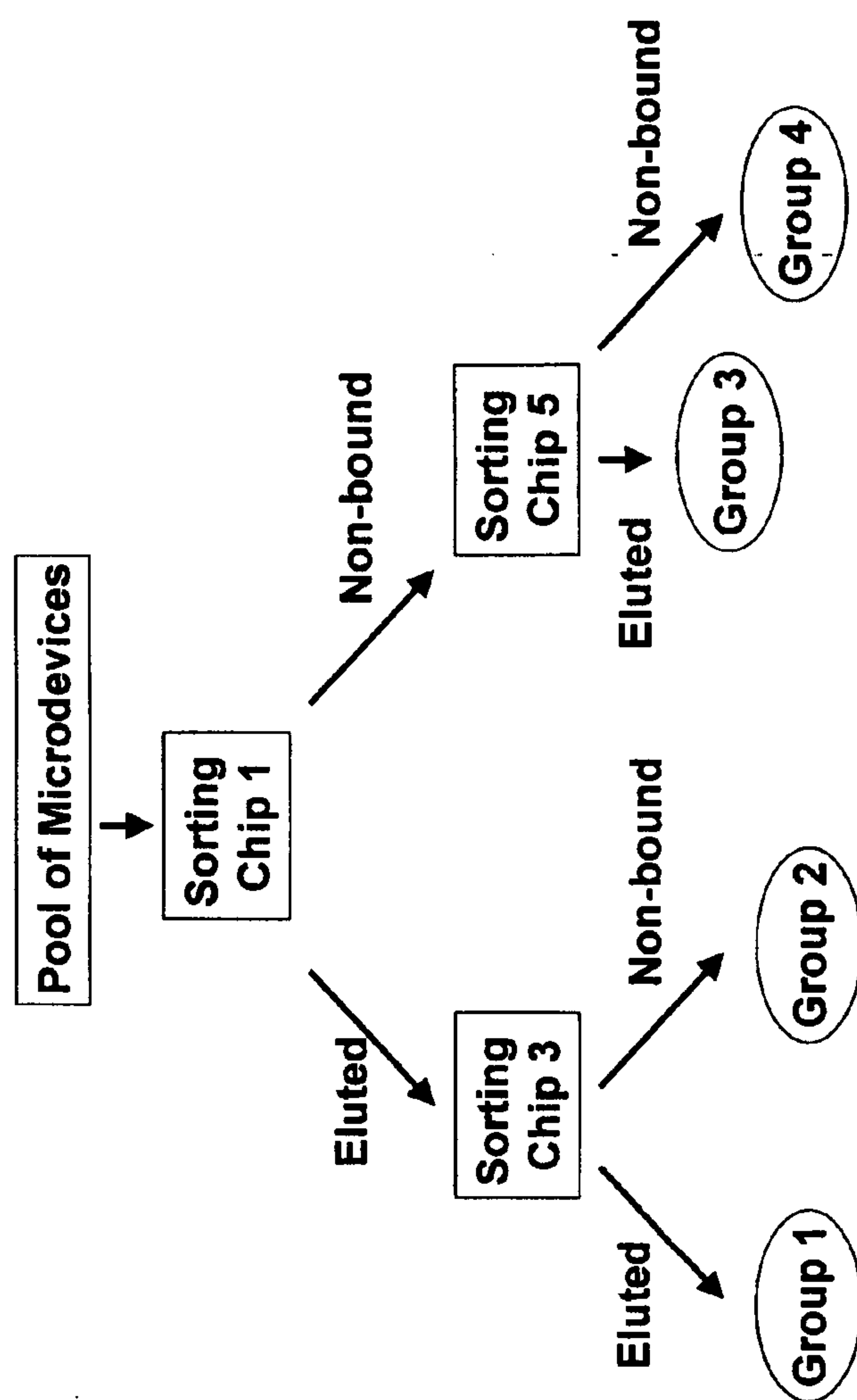
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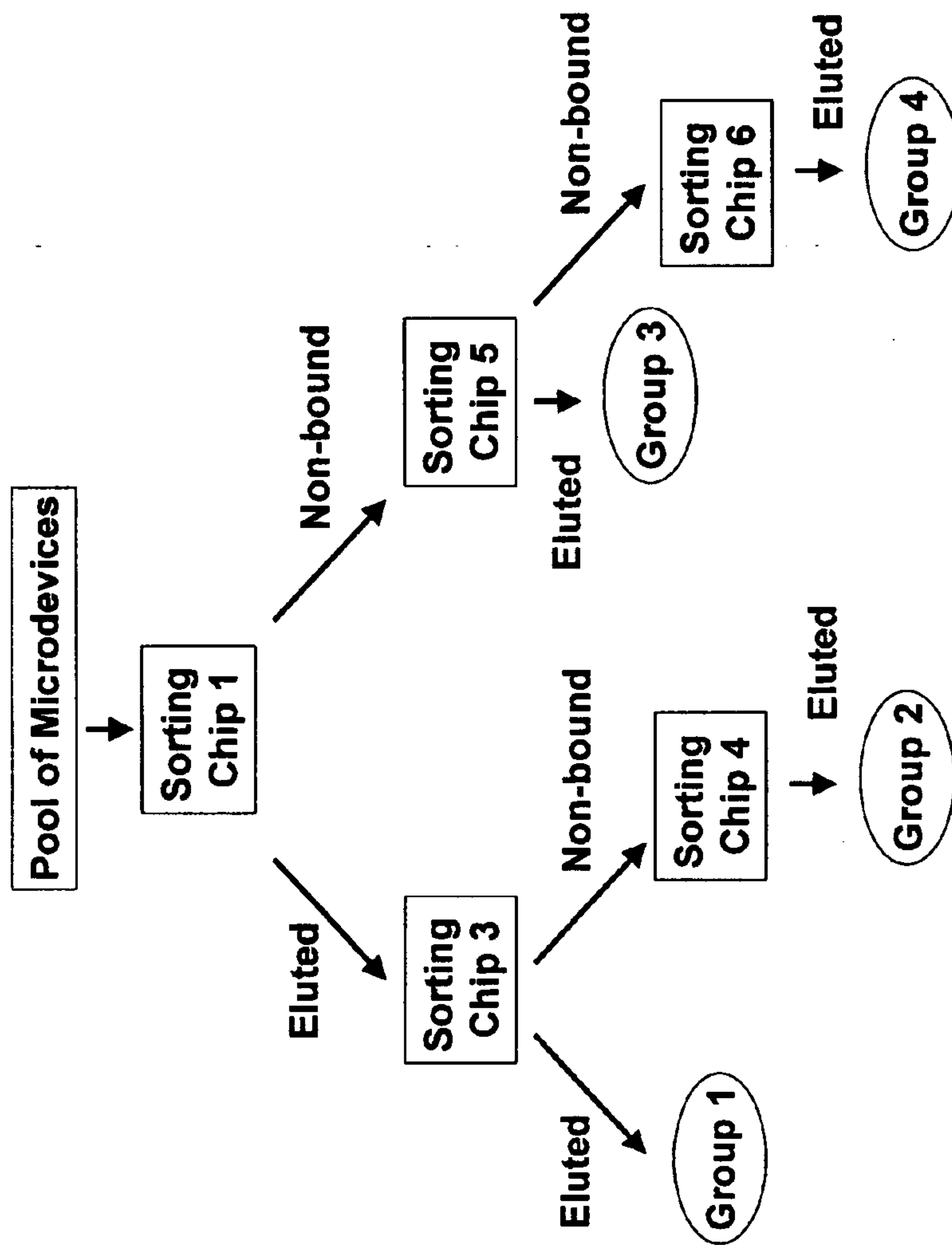
**Figure 8**

**Figure 9**

**Figure 10**

**Figure 11**

**Figure 12**

**Figure 13**

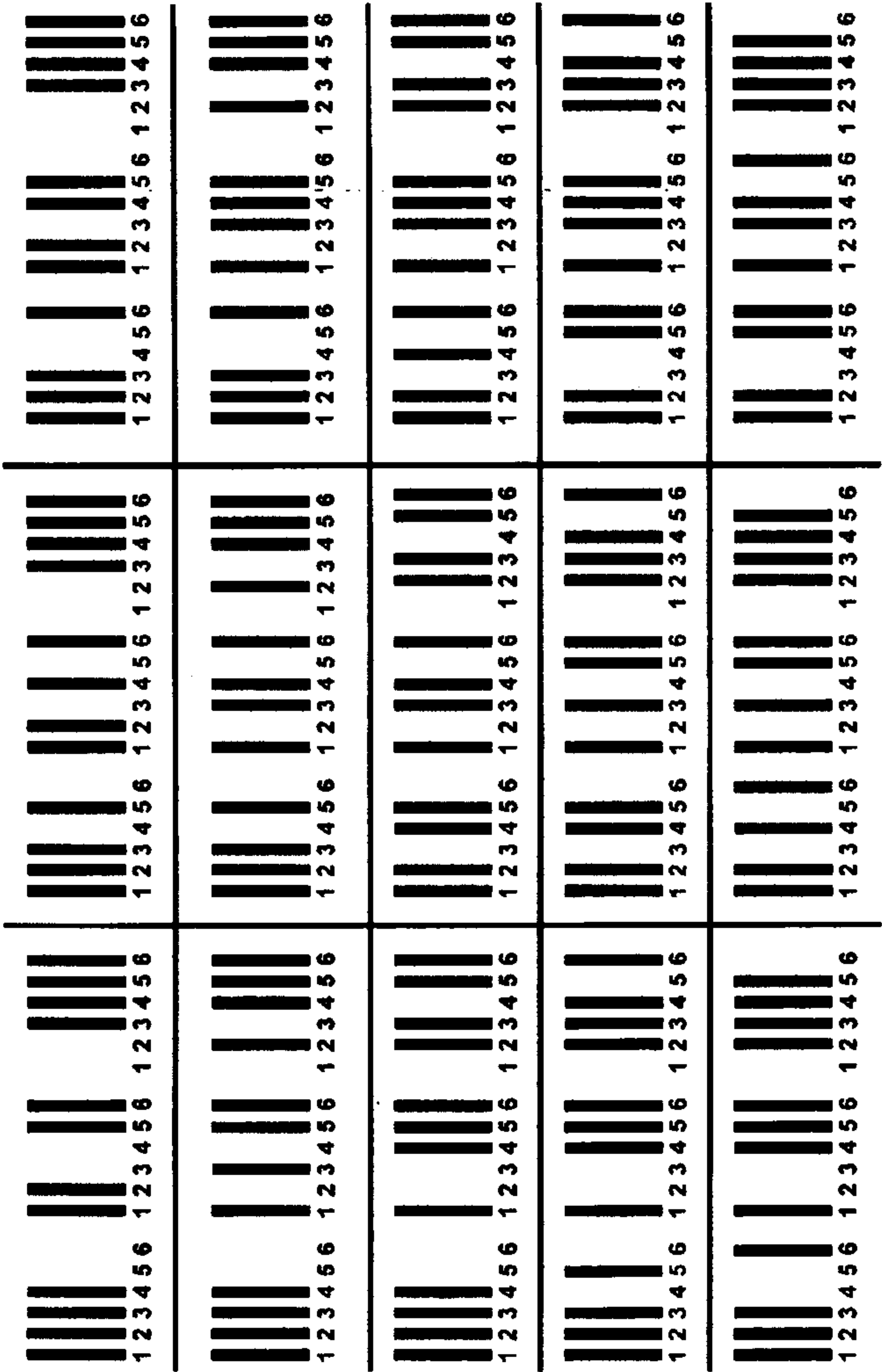


Figure 14

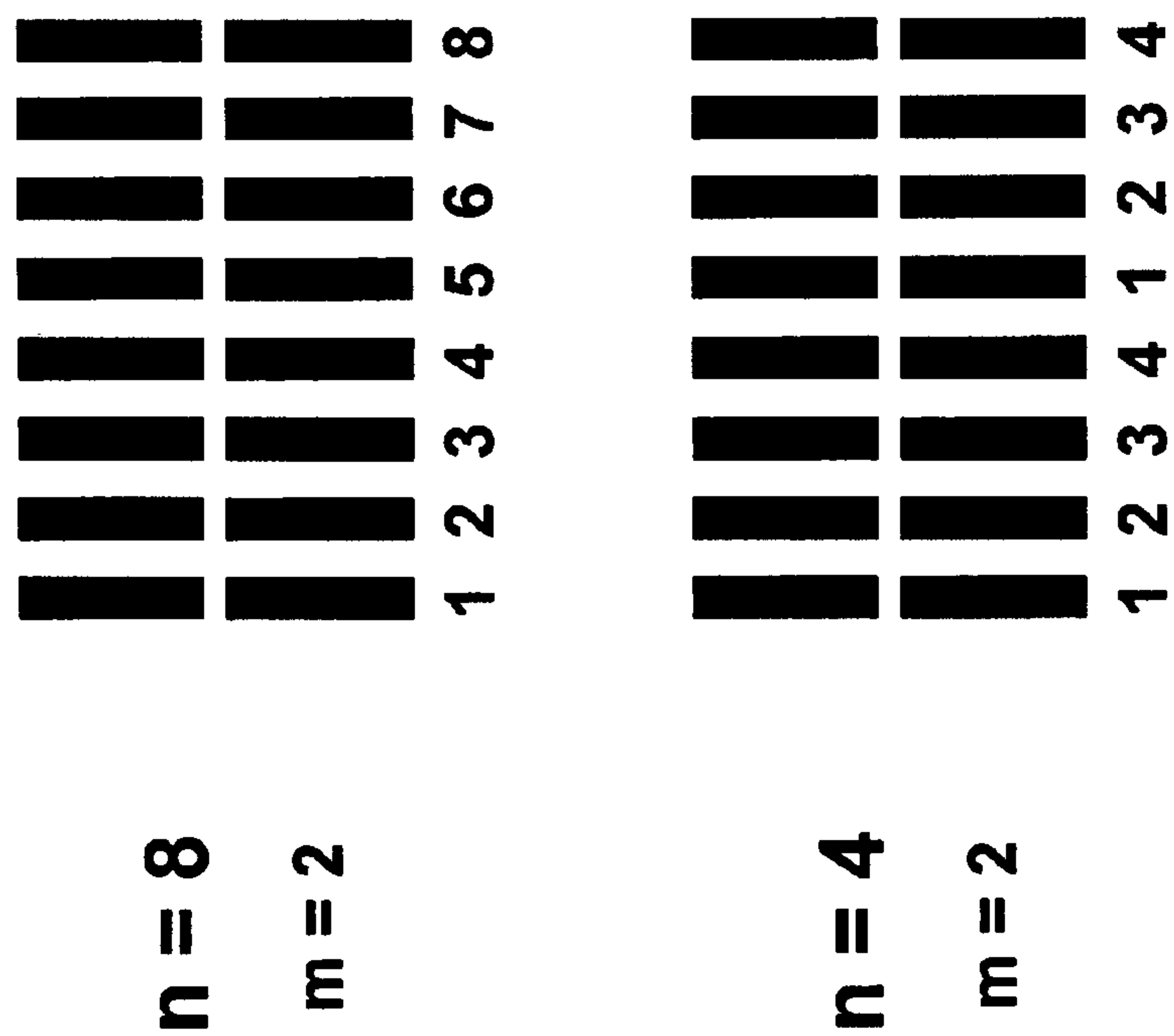


Figure 15

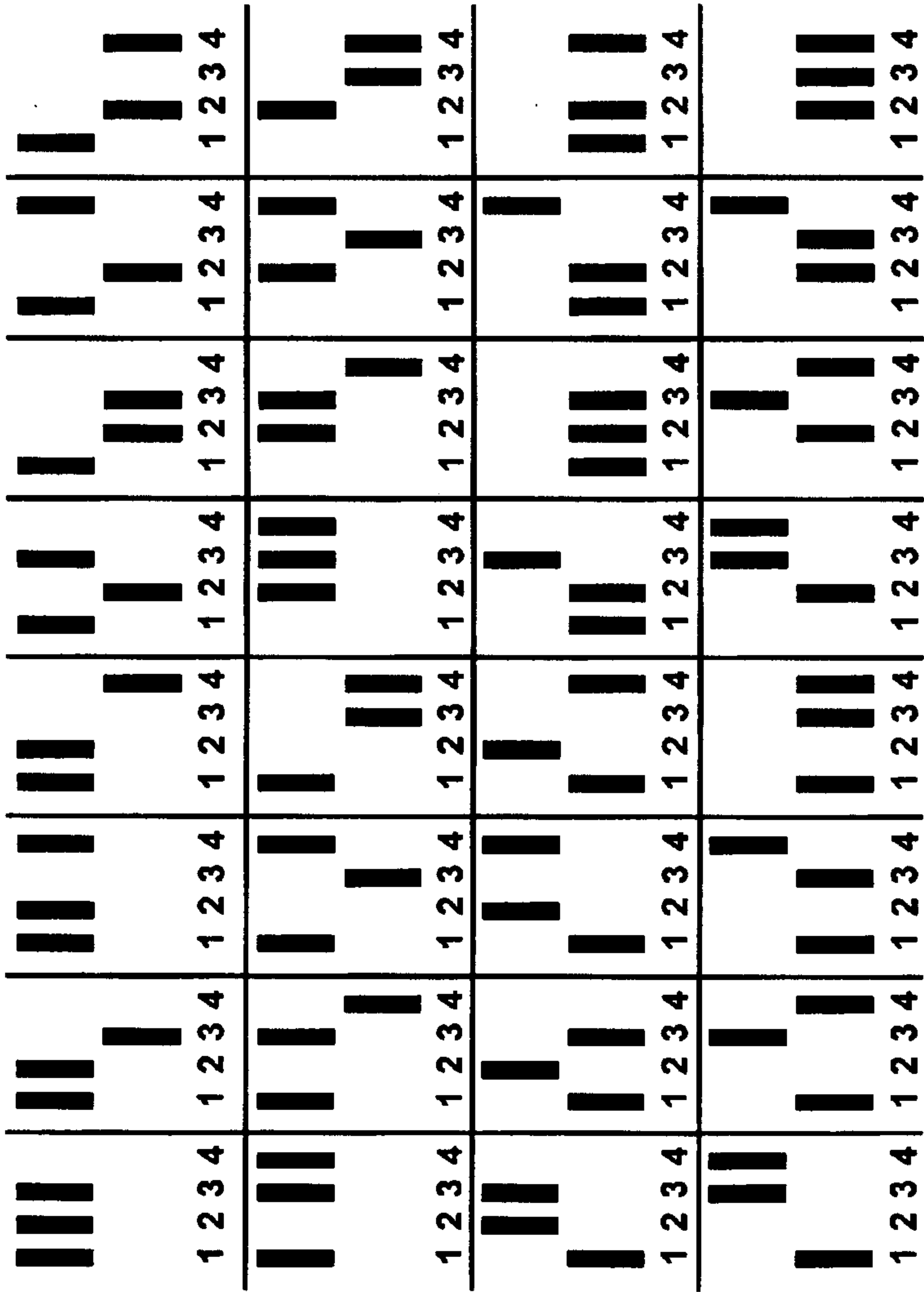
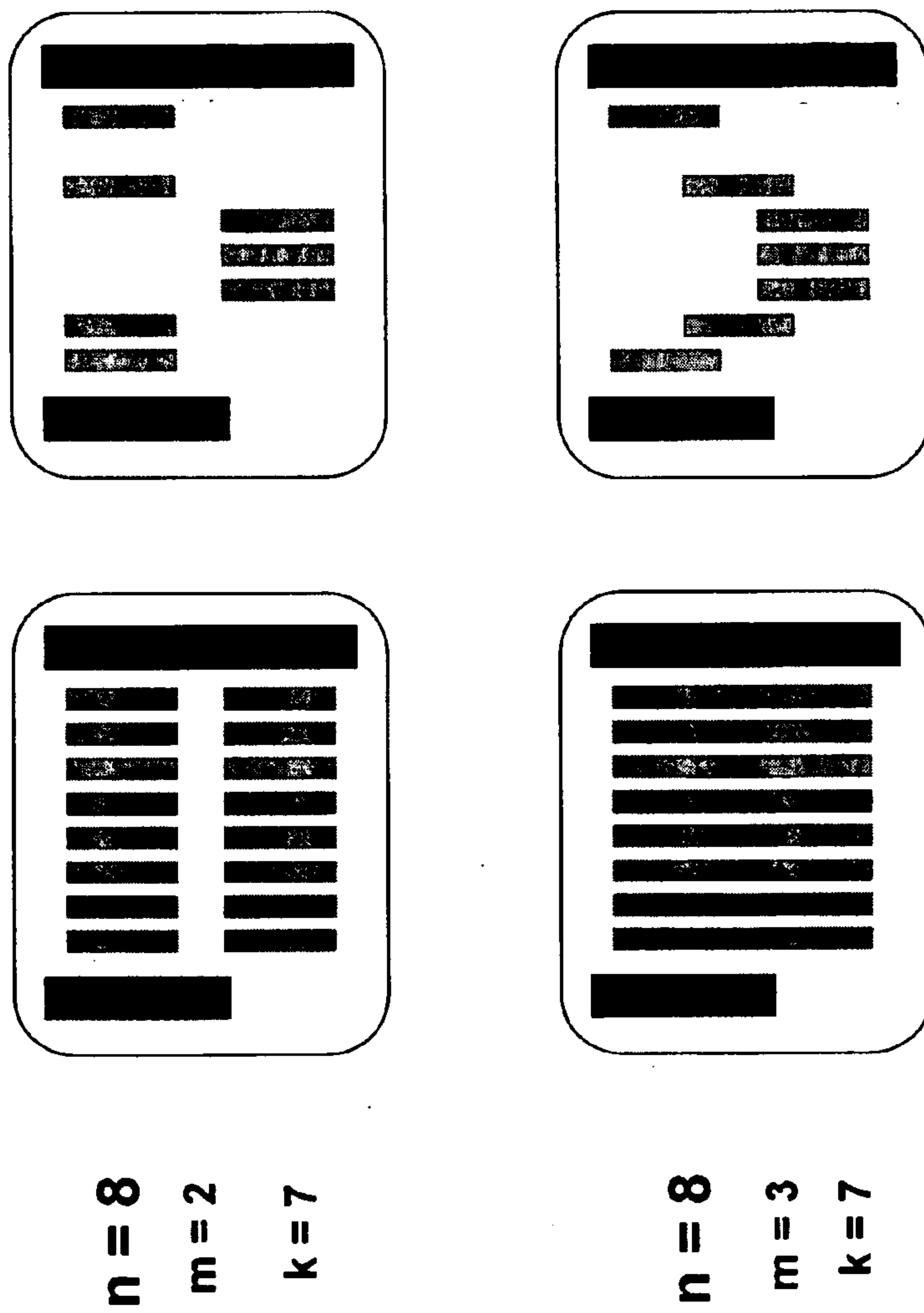


Figure 16

**Figure 17**

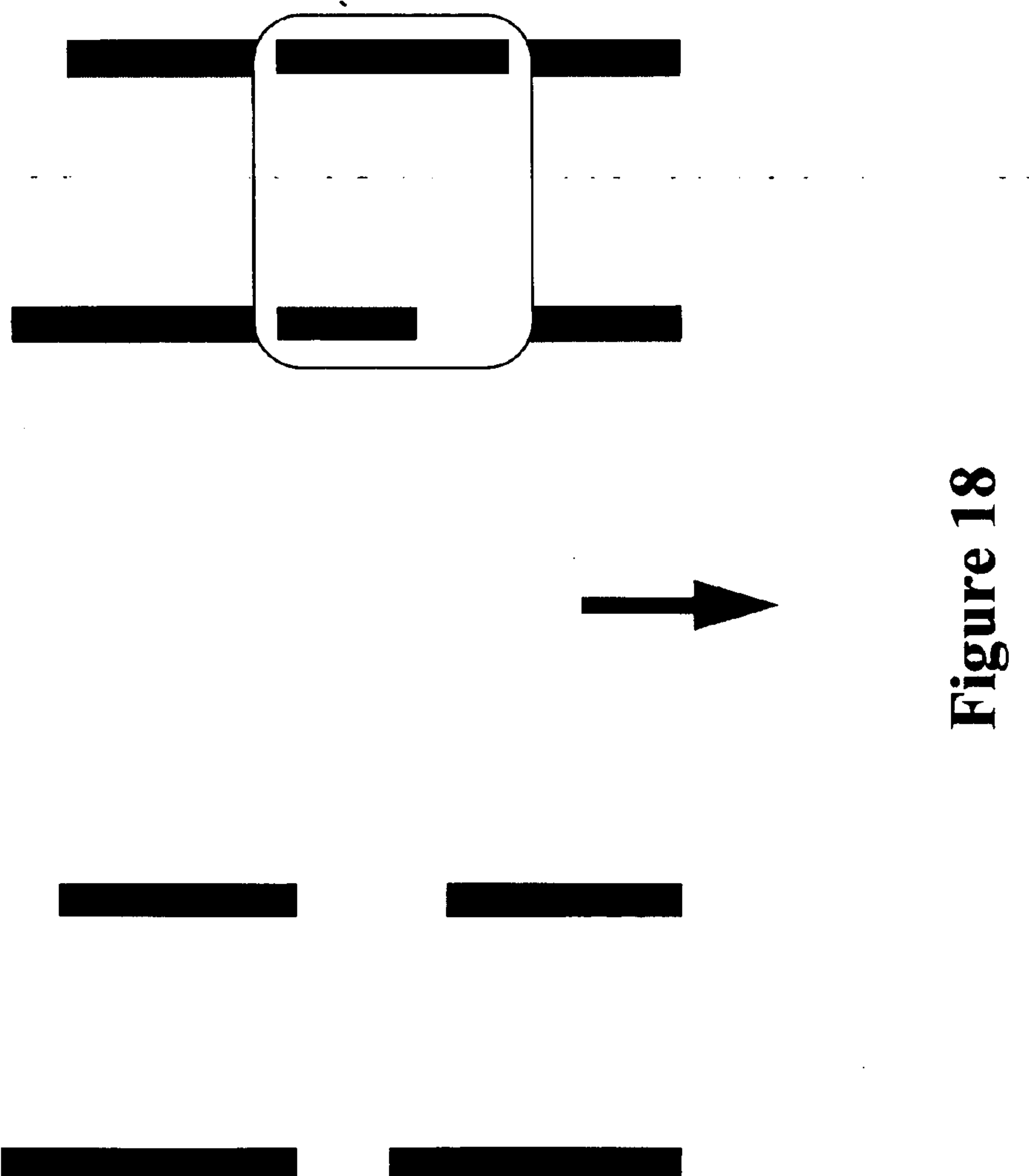


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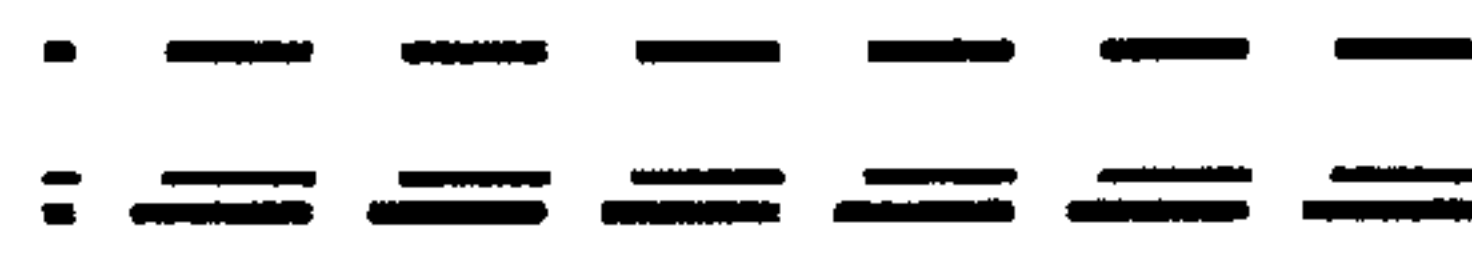
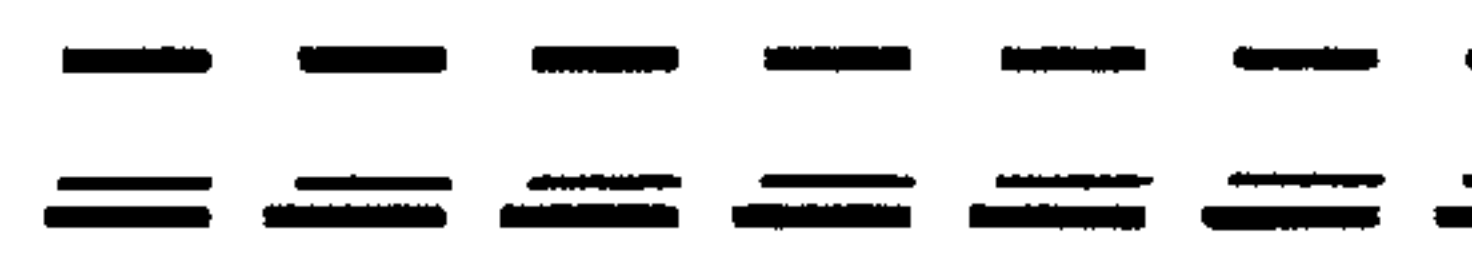


Figure 19

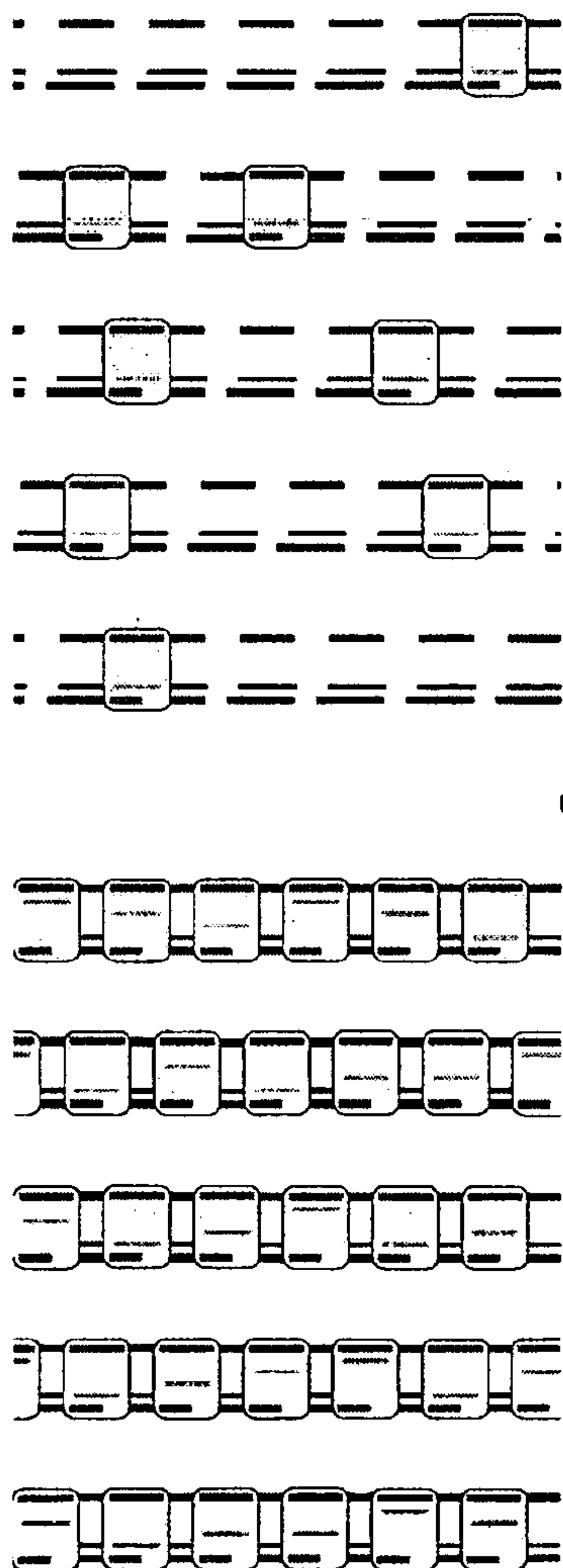


Figure 20

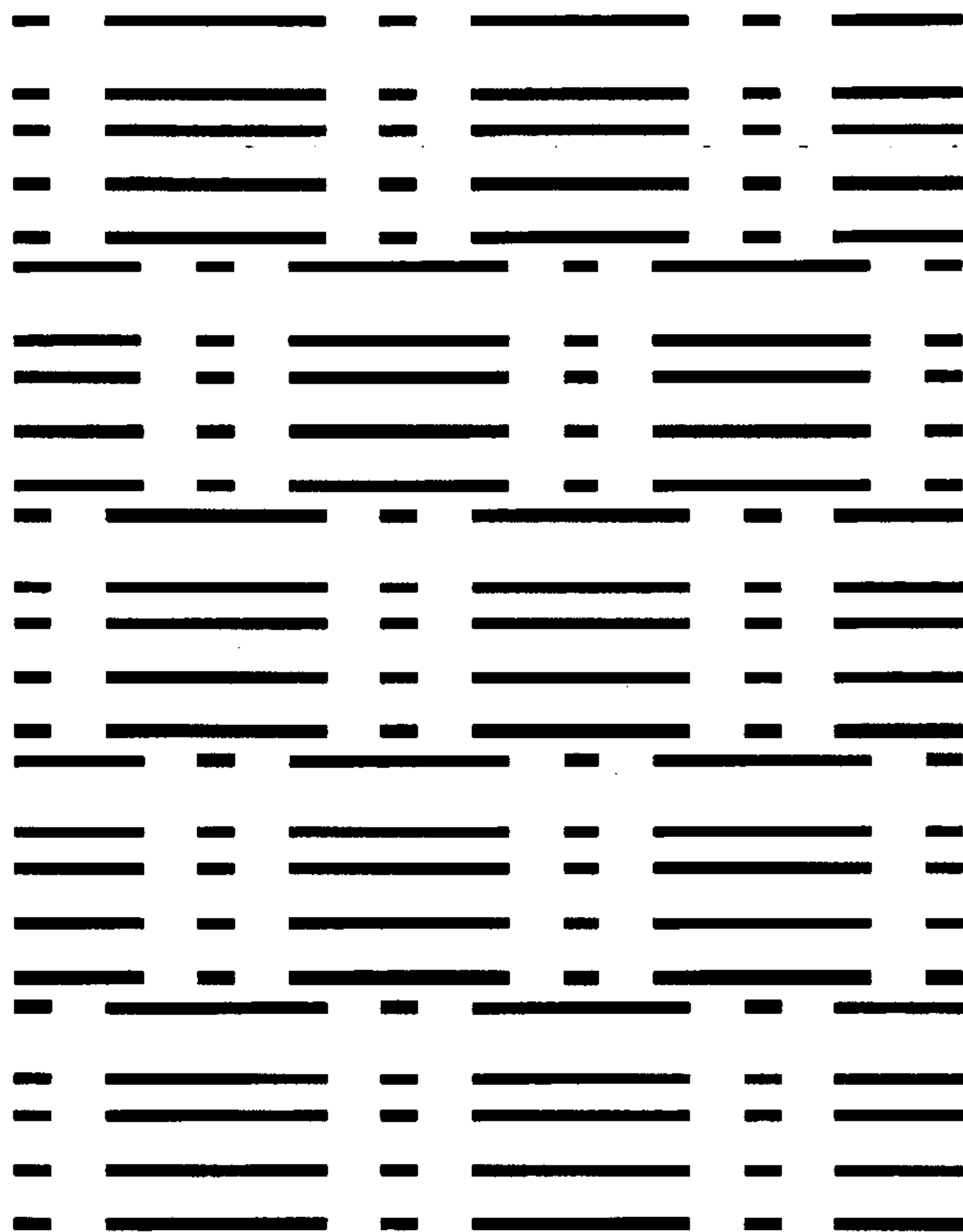


Figure 21

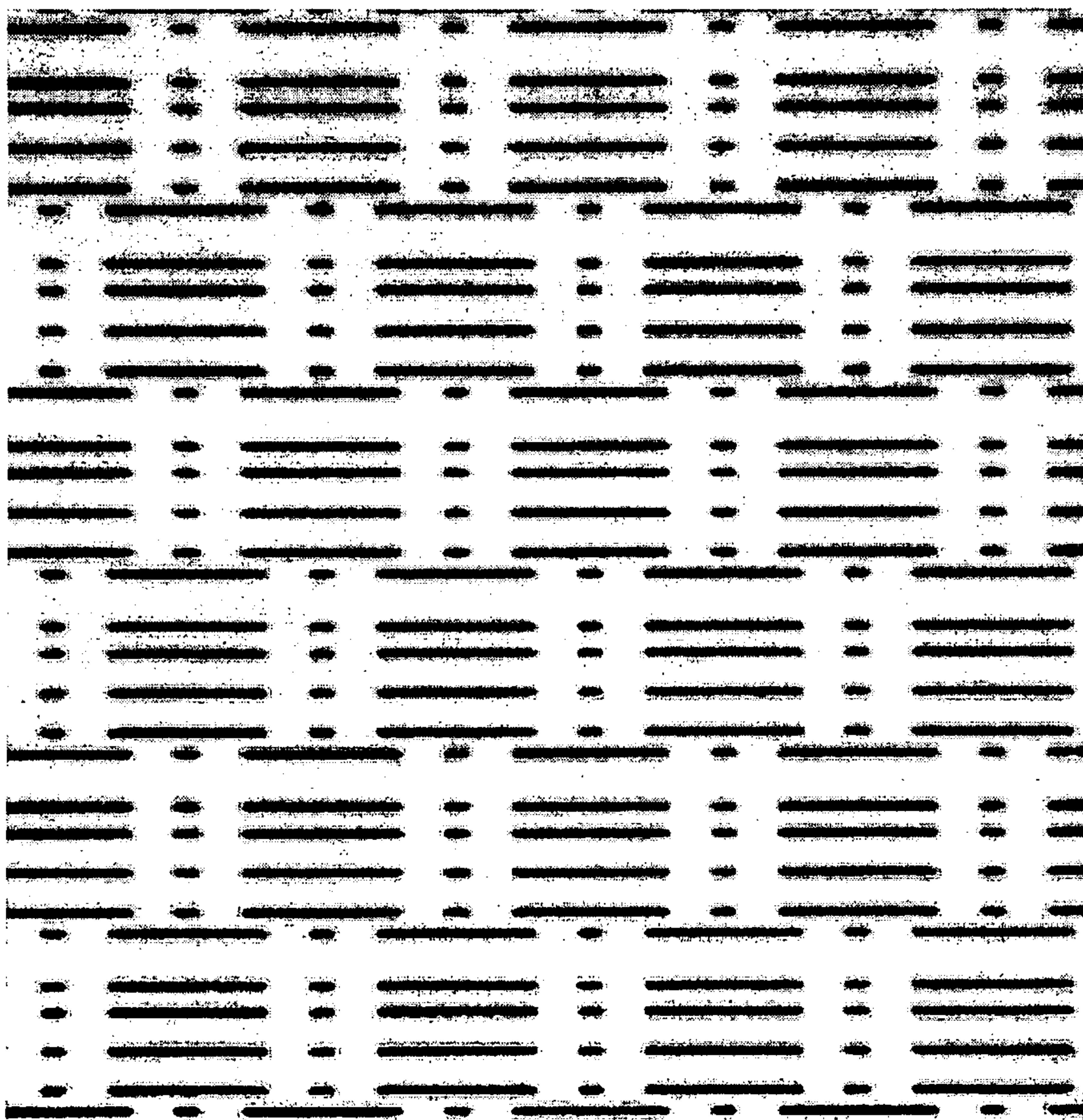
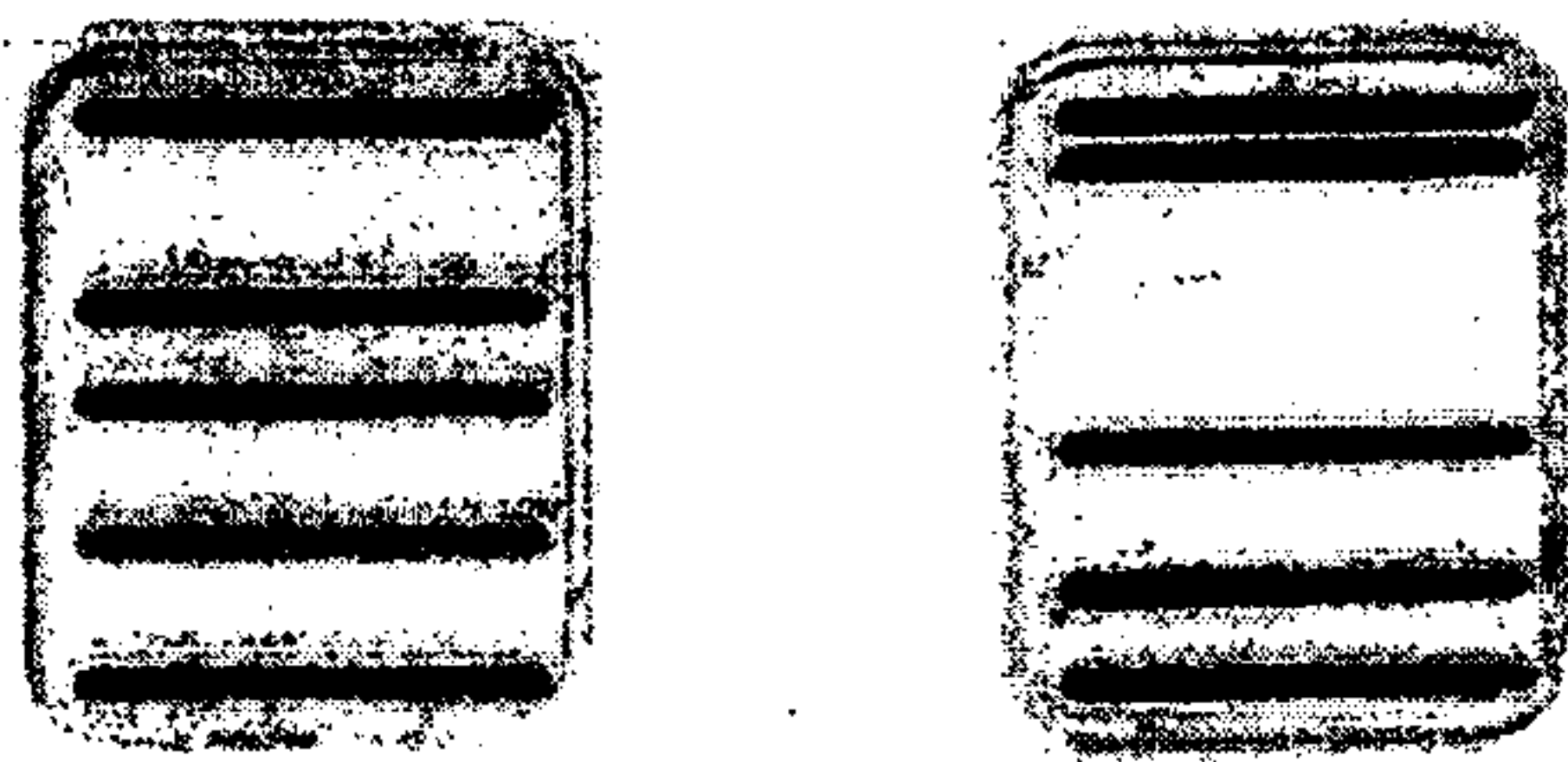


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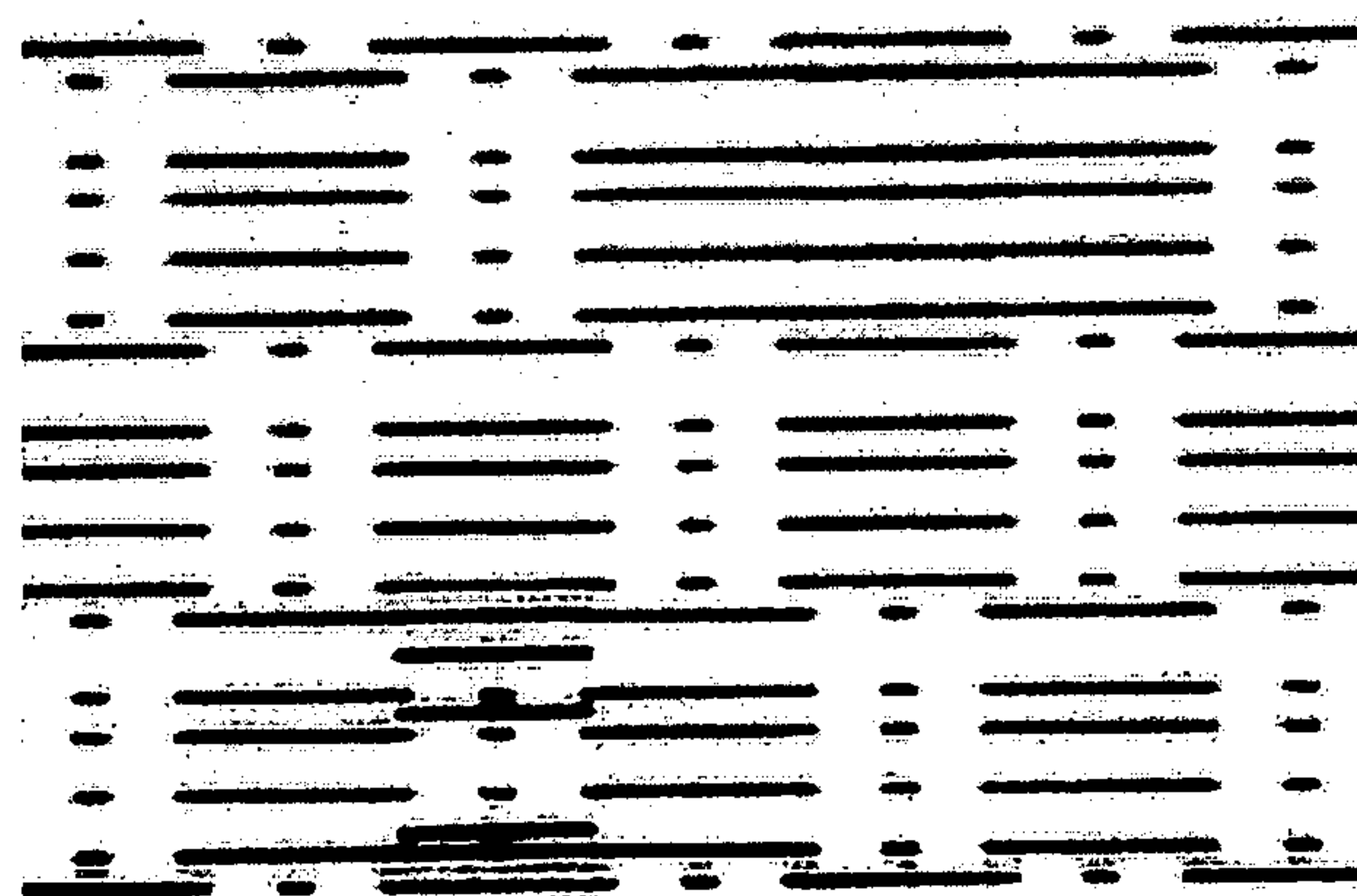
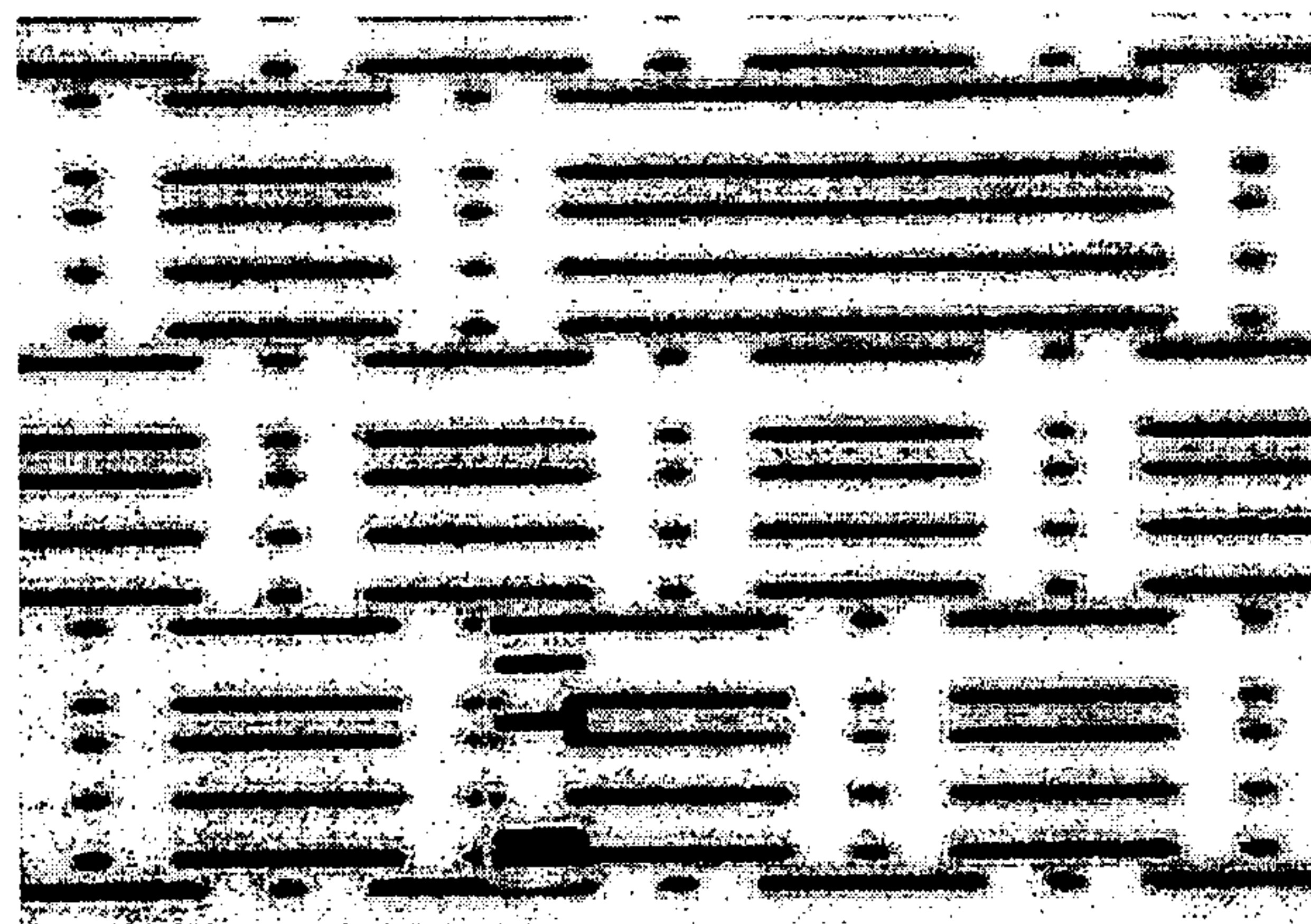
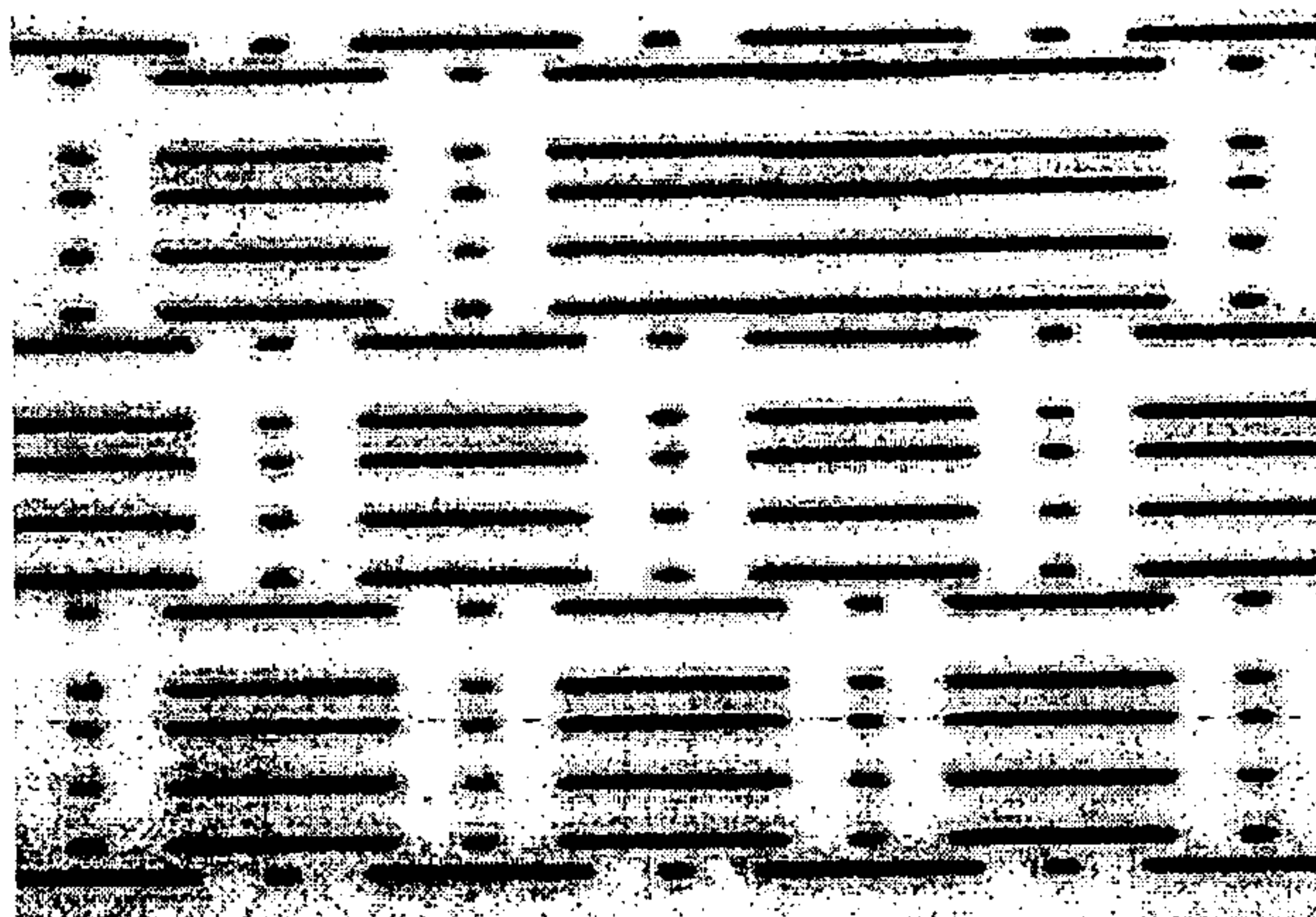


Figure 23

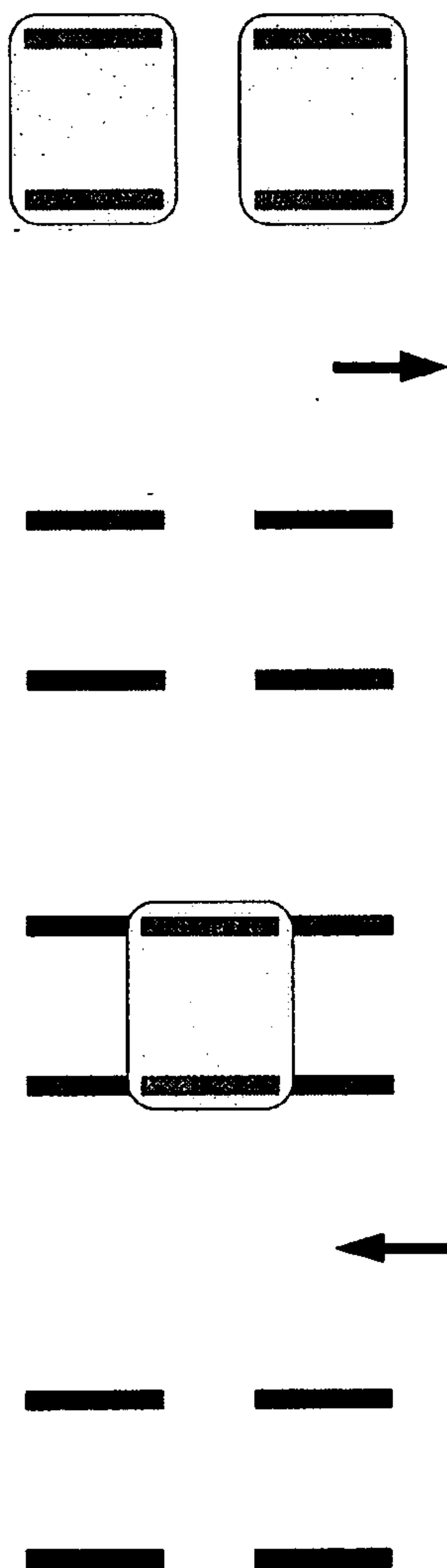


Figure 24

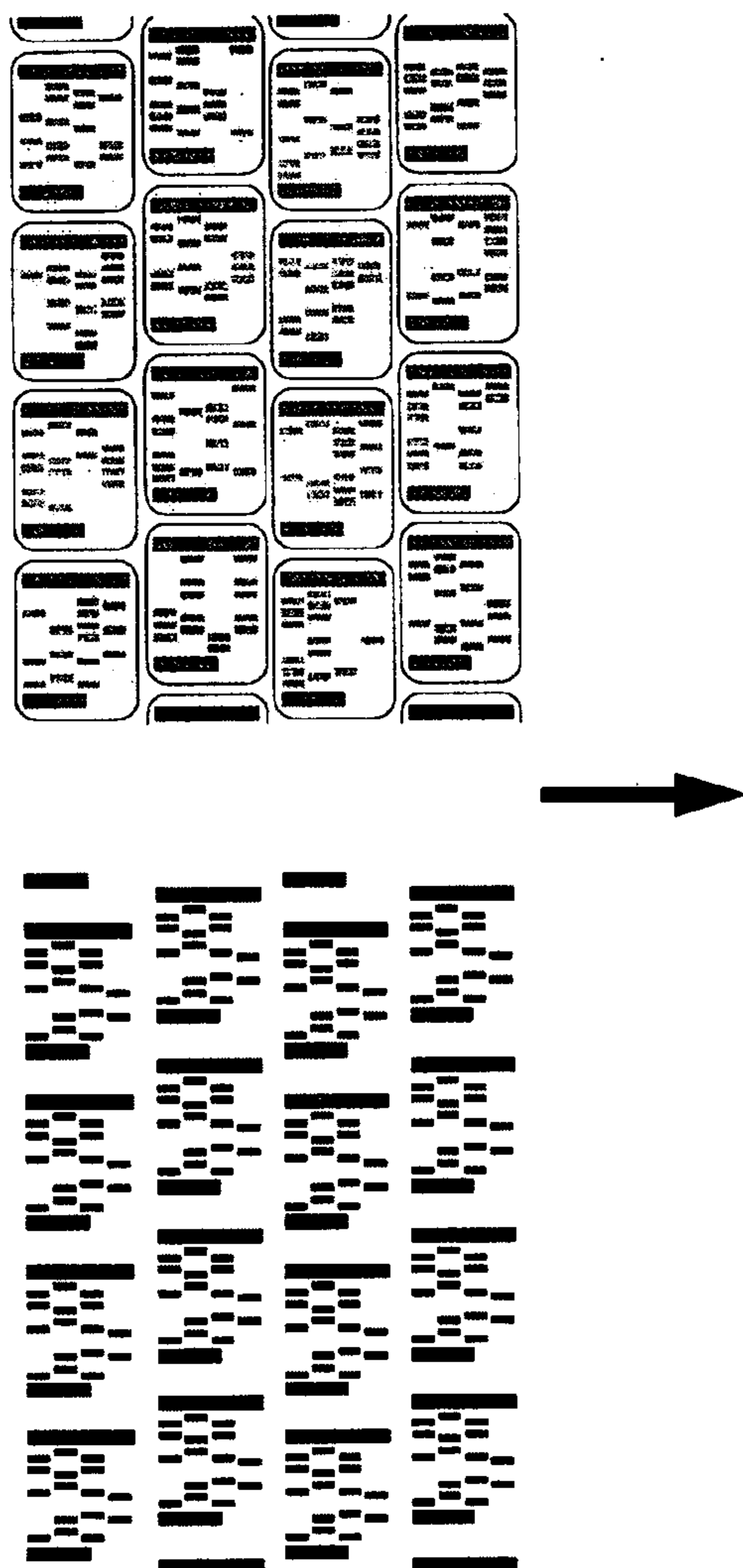
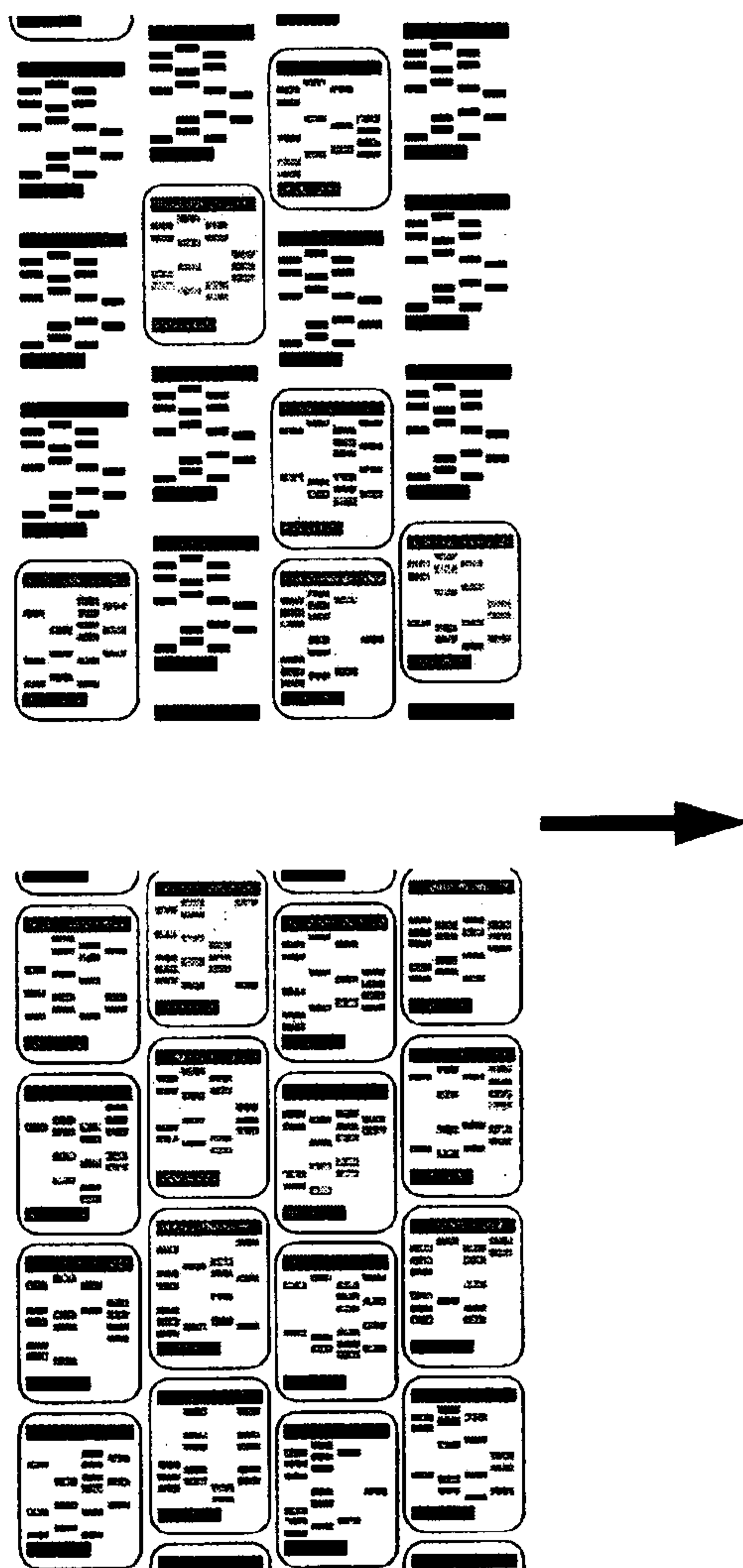


Figure 25

**Figure 26**

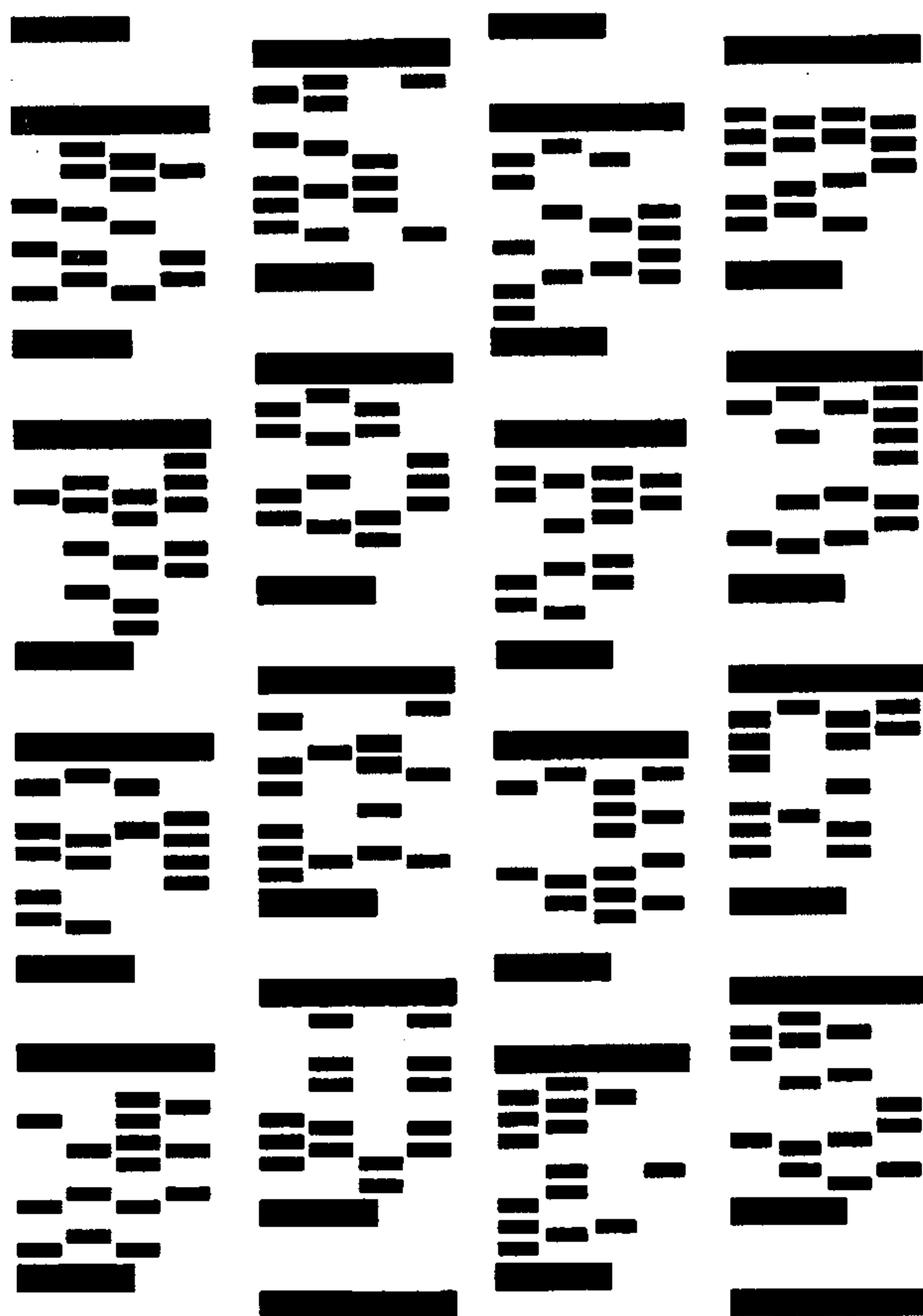


Figure 27

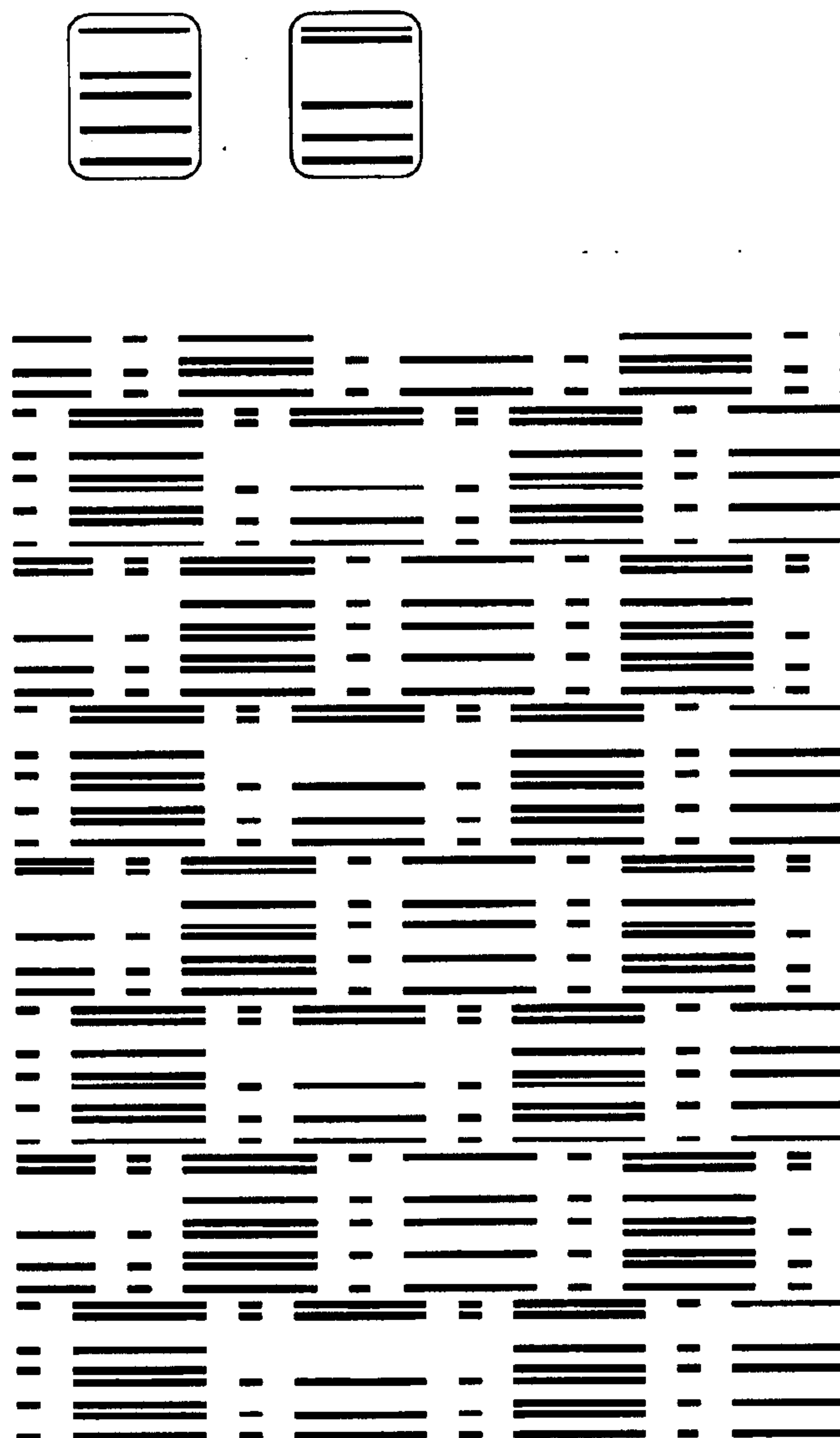


Figure 28

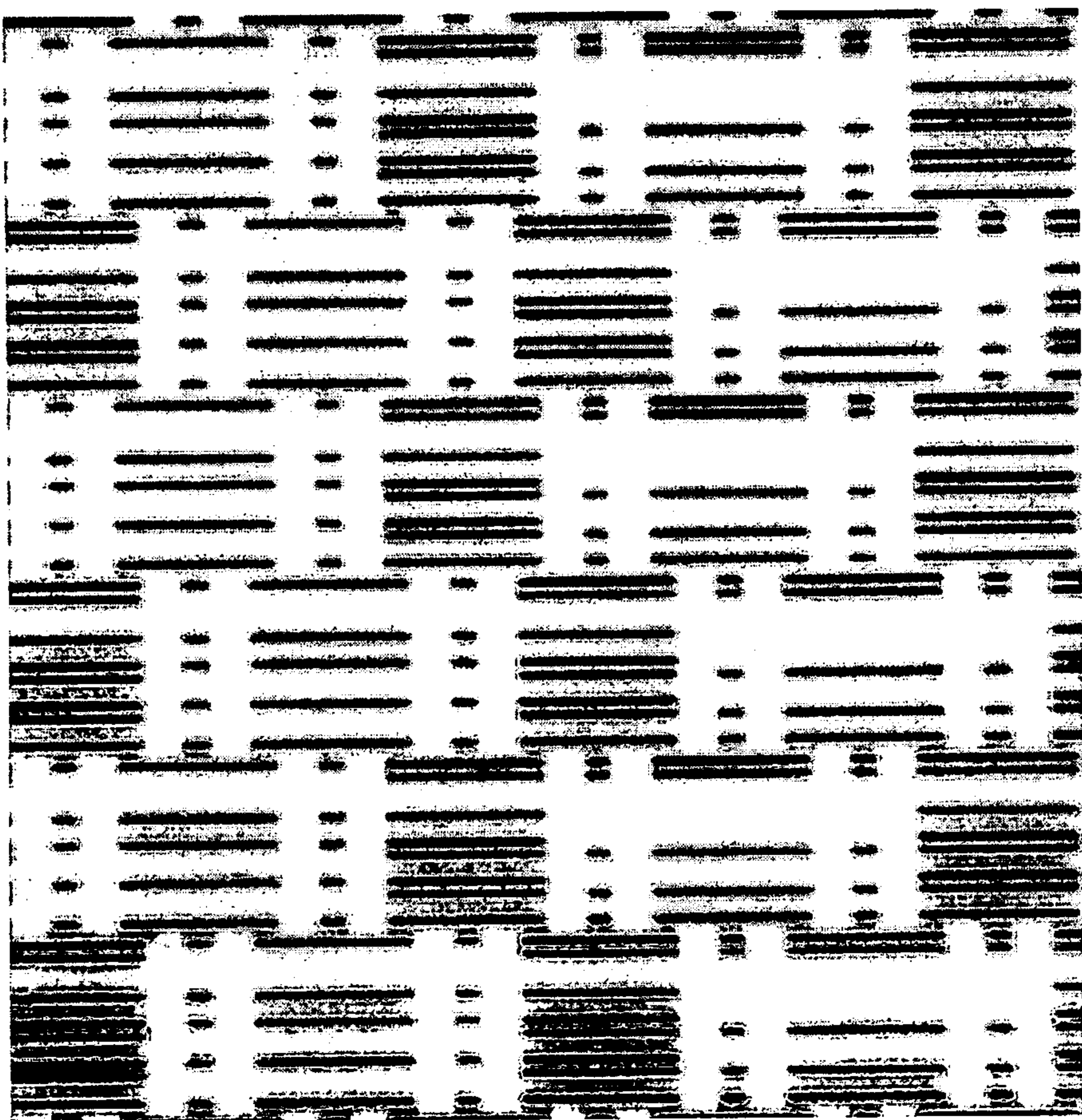
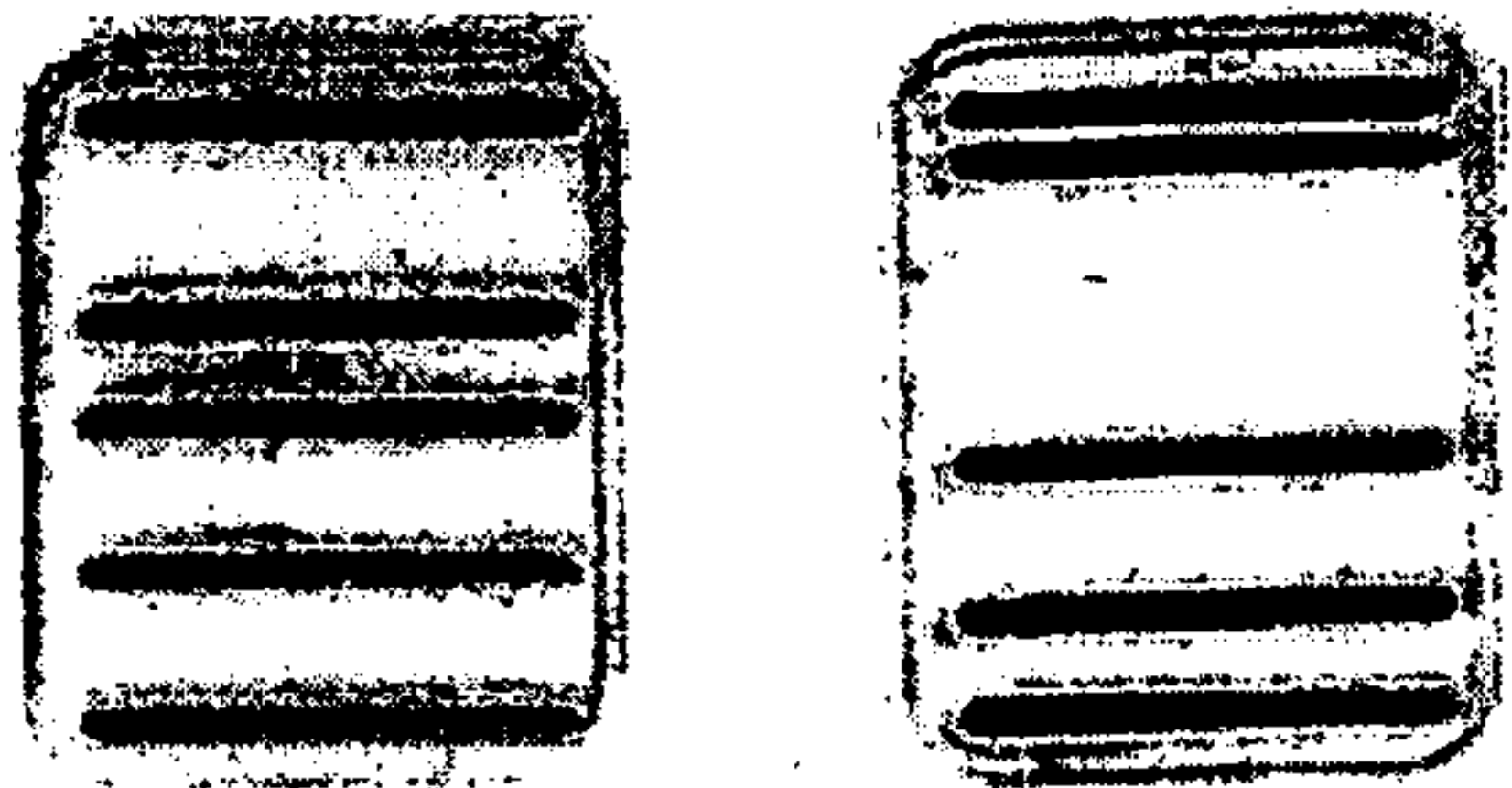


Figure 29

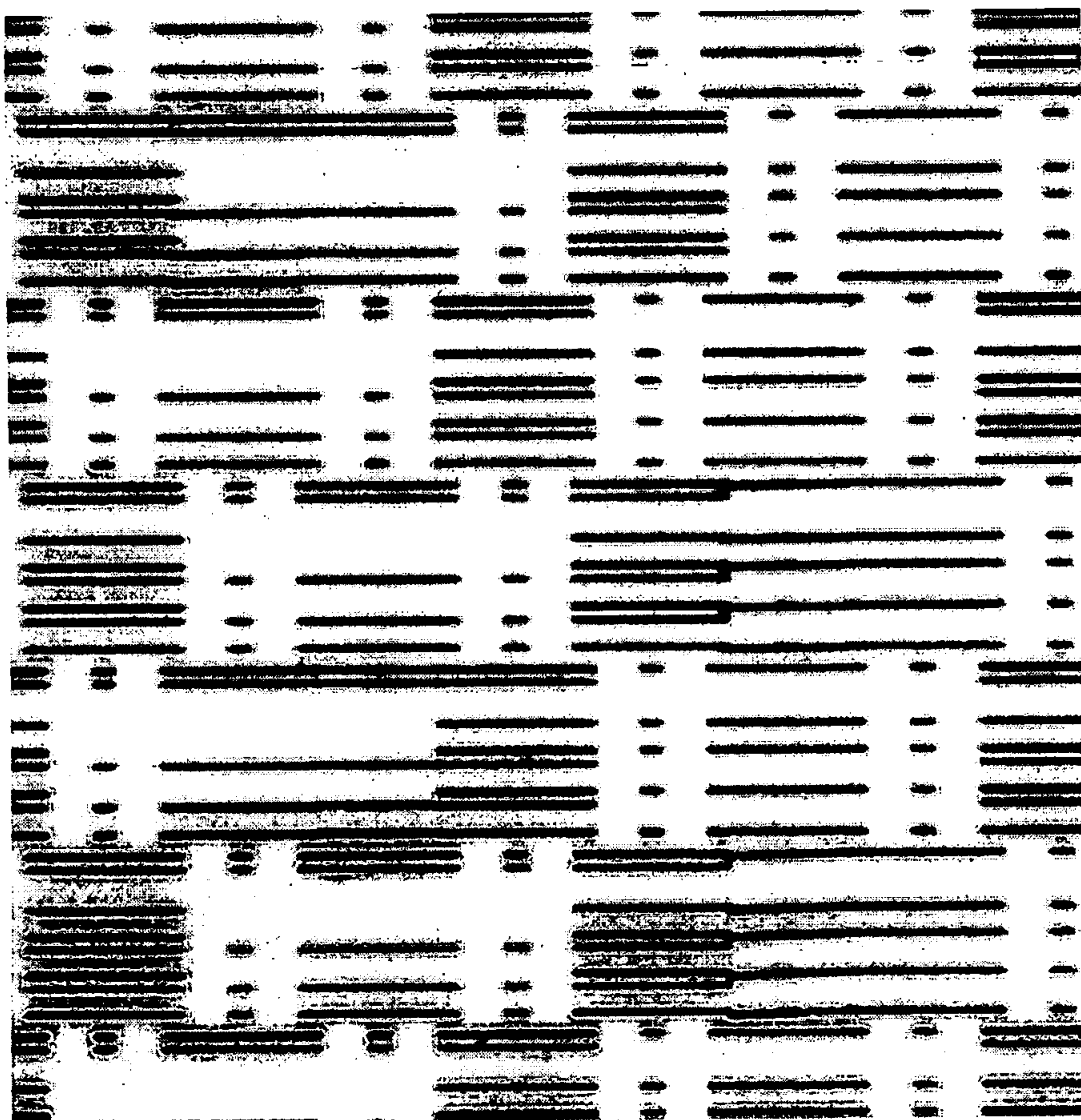


Figure 30

