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A language to describe the growth of neurites

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Abstract. How can biological plasticity been added to a simulation of neuritic growth? Coming from this question, we have chosen a new access to simulate neuritic growth under the very aspect of meaningful and progredient development of single cells. Based on a specific description-language, we have set up a computer-program, to construct neurite-models and to simulate neuritic interaction during their development. Instead of using mathematical equations, we define various types of cytoskeletons by taking a specified graph grammar. Using this technique, we are able to define strings, combined with other influencing parameters, which allow the setting up of very naturally behaving artificial nervecells, in which distinct statistical variance and fixed rules as given in DNA operate together. In this paper, we want to discuss the underlying principles of the given grammar and to show some results from these computer-simulations, which enable us to study growth, development and other specific characteristics of neurites within a simulator in comparison to in vivo-experiments.

Introduction

Classical brain research usually works on the level of microscopic analysis as well as on the level of macroscopic research on various structural levels of the cortical matter. From that structural models are extracted. In contrast to that cell biology examines the habit of a single cell with its physiological abilities to extract from this point of view their own models (Brown 1991). Both ways of research operate on the level of spatial and temporal spot checks. A direct and ongoing observation cannot take place. To find out more about the mechanisms underlying continuous developmental processes like dendritic growth, neuronal "plasticity" must be understood (Kolb and Whishaw 1989). "Plasticity" in a neurological sense must be seen as a fundamental factor within biological growth (Linke et al. 1988; Dimitrijevic 1988). – The properties, which make the difference between static or chaotic objects in contradiction to biological objects can be described as "naturalness". By that we understand an object, which is reproducible only in general outlines, but not in detail. A wheel e.g. can be reproduced exactly, while a tree, although it belongs to a specific class, is unique. This thought of naturalness links very close to plasticity. In defining this term, we subscribe to the following statement:

"... *Plasticity in the nervous system: An alteration in the structure or function brought about by development, experience or injury* ..."

Accordingly plasticity is more than an unspecific change, much more it can be understood in the following way:

1. Changes must show patterns, which make biological sense.
2. The changes must be of a positive nature. That means that they counteract against given injuries.

Because of this definition, we looked for ways describing dendrites not in a purely randomized setting or by only using probability-functions to describe various functional areas (see e.g. Letrourneau 1979).

To get a deeper understanding of how biological neural nets are set up and interact, we have simulated neuritic growth individually and corporately. Knowing about plasticity of neurons, where e.g. informationally relevant part grow or shrink, we have put our emphasis on spatial effects, especially during the period of embryonic growth (Brandt 1981). We have set up computer-simulations which allow an interacting growth of various nervecells, coming from different genotypes and produce a set of phenotypes, which depend not only on the various genotype-information, but also on external factors, general and local age as well as on influence coming from other cells. By using given code sequences similarities to DNA in terms of containing long code-sequences can be found. These sequences, can be understood as genotypes and contain the entire layout of the forthcoming object.

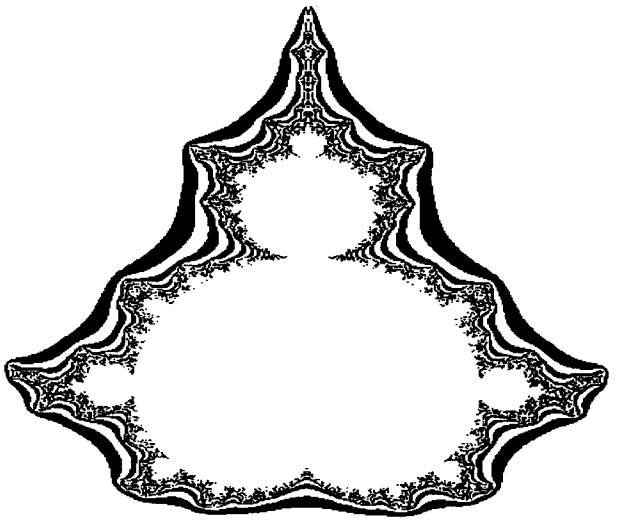

Fig. 1. Mandelbrot's Apple Man

In simulating nerve growth, we had to recognize, euclidian geometry, which only speaks of the basic forms like cycle, rectangle, etc., is not a good starting-point. The objects needed for our simulations are much more of fractal nature, which allows to some extent the taking into consideration of the irregularity of living objects (Barnsley et al. 1989). Taking e.g. Mendelbrot's "Apple man" (see Fig. 1), we can find a general structure, that shows close relationship to contours within nature (Mandelbrot 1980, 1984). We discovered as a fractal subquantity that so called "Rewriting String-Systems" (Aono 1984). In our own research, we have started to use this method to generate the primary dendritic tree and use the resulting information to add further details. Discrete interaction (Skoff and Hamburger 1974) of specific cell areas with other totally different structured celltypes were included (e.g. Growth-Cones (Davies 1986; Purves 1988) with developmental physiology). The aim of our computer based models is a deeper understanding of neuronal interaction, by studying the development and growth of these nervecells. Our main emphasis is put onto the spatial development and the interaction of several nervecells.

Thus we want to contribute to the discussion within artificial neural net research, following Carver Mead's (Schrade 1989) ideas, who talks about neuronal architecture instead of pure random-modeling.

1 The concept for rewriting-graph-grammar

Our works derive from the "Lindenmayer-Systems". They were introduced by the the biologist Lindenmayer in the late 1960s (Lindenmayer 1968a, b). He used these rewriting string systems to simulate the growth of plants. Since that time, the L-System has got an important place in various areas as the theory of formal languages or biomathematics. This technique was used to describe the growth of cells within plants, but not to describe dendritic growth. The basic idea of graph-grammar is that initially a word put together out of letters of a defined alphabet is given. Secondly there are exchange-rules, where a specific letter is replaced by an attached word. When the process of rewriting is launched, sequentially each letter of the initial word is replaced by the appropriate exchange-word if there is one, otherwise the letter is exchanged by itself. By this process a new chain of letters if produced (Prusinkiewics 1989).

This process must be repeated a given number of times, whereby the number of iterations plays a major role in the resulting structure. Once the rewriting process is finished, the given chain of letters can be used to run a type of turning-machine, which in our case is a two-dimensional drawing-unit. To accomplish this, the letters of the alphabet must correlate to special actions like move forward, turn right, turn left, save current information, restore current information etc. As this information is still not enough, it is necessary to predefine values like the real length of a way **S** or an angle **a**. This drawing process only operates on defined operations, all others are ignored.

1.1 An example

The following example shows the rewriting-process for a period of four iterations. An initial word, the number of iterations and a number of exchange-rules, called productions, are given. Whenever an exchangeable character occurs the very letter is taken from the primary chain and replaced by the relating set of characters in the secondary chain. All those letters, which are not linked to a 'production' are just copied to the new chain. The process runs sequentially. Once all characters are put to the target the setup of the new generation is finished.

1. An example for the rewriting process

The use defined input

inital word:	$X+F-[X]$
1. production:	$X \rightarrow Y[F-F+]$
2. production:	$Y \rightarrow FZF$
3. production:	$Z \rightarrow +[X]-$
Number of iterations:	4

The rewriting process:

At the beginning: $X+F-[X]$

1. generation: $Y[F-F+]+F-[Y[F-F+]]$
2. generation: $FZF[F-F+]+F-[FZF[F-F+]]$
3. generation: $F+[X]-F[F-F+]+F-[F+[X]-F[F-F+]]$
4. generation: $F+[Y[F-F+]]-F[F-F+]+F-[F+[T]F-F+]]-F[F-F+]]$

Stripping the chain:

Original: $F+[Y[F-F+]]-F[F-F+]+F-[F+[Y[F-F+]]-F[F-F+]]$

usable chain: $F+[F-F+]-F[F-F+]+F-[F+[F-F+]-F[F-F+]]$

Understanding the chain:

$F+|F-F+$
$\quad |-F \quad |F-F+$
$\quad |+F- \quad |F+ \quad |F-F+$
$\quad\quad\quad\quad |-F \quad |F-F+$

2. Meanings of various characters, which are needed to run the drawing unit

F – Move pen forward one step in current direction and draw line
f – Move pen forward one step in current direction without drawing
+ – add α to current angle
− – subtract α from current angle
[– put current plot-information onto the computer-stack
] – reset plot-information to last stack-information

What is going to happen, once the final number of iterations has taken place? In a second step, the produced chain will be used to run a drawing facility. Starting from a defined location and direction a virtual pen is directed by specific characters of the given chain. As shown in Box 2 a number of symbols contain specific orders for shifting, moving or jumping of the pen. Any unknown symbols, which remained from the rewriting process are skipped. Only defined letters will affect the drawing-process. The following list shows those symbols which are currently in use, all other symbols are ignored by the drawing-system

2 Adding further components

2.1 From tree-type to cell-type objects

Based on the given syntax, we had to see, that with the given technique, the typical architecture of dendritic tree as evident from microscopic preparations could not be defined completely. Because of this, a specialized operation had to be added. This "*H*-operator" functions as a "cellbody" which is characterized by the following features: *1.* It is the center of the entire growth process. *2.* One axon with a given structure can start its growth from here *3.* optional *n* dendrites start growing from it, whereby the initial directions of the various identical dendrites is spread over a given angle-area. Figure 2 shows a completely simulated cell. The triangle in the centre marks the cellbody. Around the cellbody several dendrites of one structural type and one axon of a different type can be seen. Comparing this picture with those "trees" drawn in Fig. 7 the value of this operation becomes evident. "Trees" of the type as shown in Fig. 7 start e.g. at the bottom (instead of starting in the centre). They are not able to produce more than one type of twig from the initial point.

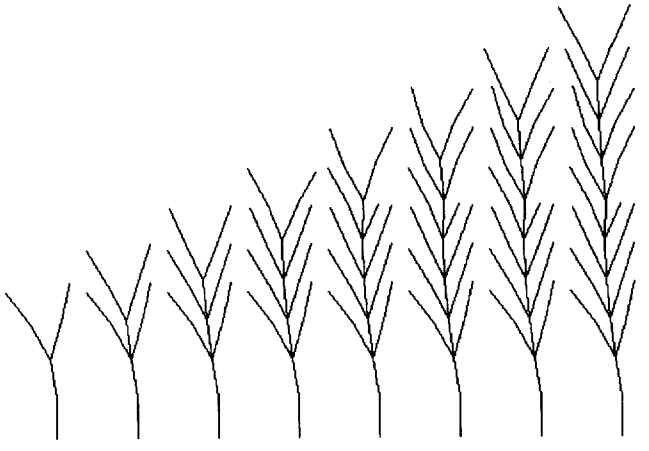

Fig. 2. Developing "tree", defined by: Init: $\langle X \rangle$, Prod.: $X \rightarrow XFY$, $Y \rightarrow [-FF][+FF]$

2.2 Growth-operator

In the context of growth, another obstacle must be referred to. The way rewriting-string operation works gives each character only one chance to influence the resulting picture. If each way-increment is understood to be one small segment of the growing object, it becomes evident, that the growth of this segment occurs more than once. Moreover the growth-factor depends on the number of former growths and on a timescale. Consequently we included a specific character, which allows this type of growth, were a relation between the growthlength and the number of prior uses if given by:

$L_i \sim 1/n_i$.

where L_i is the actual length and n_i is the number of times, this operator was prior in use.

2.2.1. To get a better understanding about the differences and consequences deriving from the '*G*'-operator in comparison to the static '*F*'-operator and a specific production $Z \rightarrow ZF$, Figs. 3–5 show the results coming through these different operators. In all of the given examples the production *X* and *Y* are kept similar in being:

$\mathbf{X \rightarrow XqY}$, where *q* stands for '*F*', '*G*' or '*Z*'

$\mathbf{Y \rightarrow [-qq][+qq]}$

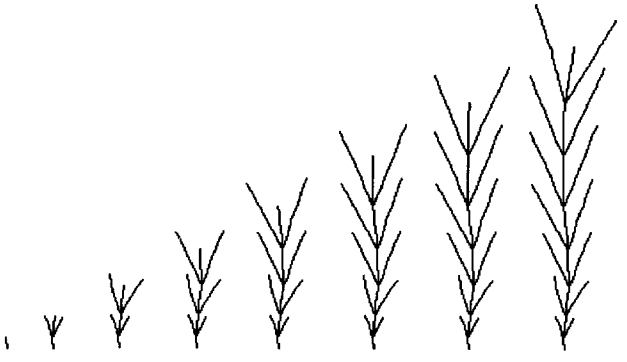

Fig. 3. Developing "tree", defined by: Init: $\langle X \rangle$ Proc: $X \rightarrow XZY$, $Y \rightarrow [-ZZ][+ZZ]$, $Z \rightarrow ZF$

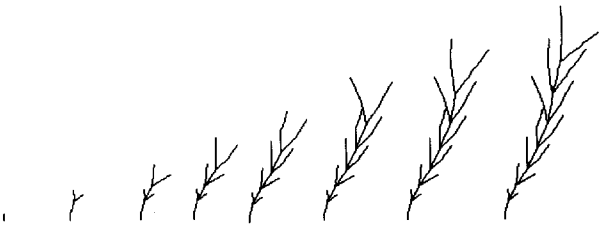

Fig. 4. Developing "tree", defined by: Init: $\langle X \rangle$, Proc.: $X \rightarrow XGY$, $Y \rightarrow [-GG][+FF]$

Fig. 5. Drawing of an cell-type object

The '*Y*' -production makes symmetric branches from the stem, while the '*X*'-production increases the step and includes further sprouting-points. A comparison of these three types shows in the first example, that the operator '*F*' produces a static branch without any possibility of change. In using the production *Z* the situation becomes different, because each iteration another '*F*' is added to each branch. The disadvantage of this operator is, that no change of length can take place, nor is there any chance of stopping this process. The third example shows that this object looks very similar to the one before. Yet the important difference could be observed at a higher number of iterations. Figure 5 shows, that the outgrowth of the older twigs is gradually reduced, until no further growth takes place. This cannot be found in Fig. 4!

3. From genotype to phenotype – growth influencing factors

3.1 Mutations

Using this type of grammar gives the chance of including mutation effects into the growth of the dendrites. Understanding the initial strings and the productions as the biological genotype, the phenotype is created by internal and external factors, as given by mutations or the rewriting-process itself. In biology mutations can be understood a changing some genomes of a cell, randomly triggered by different processes. We have taken this idea and included it into the rewriting process, which means that once a specific mutation took place

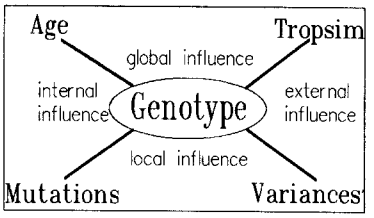

Fig. 6. Factors influencing the makeup of the phenotype

all following rewriting processes will have to live with the change.

3.1.1 Erase-mutation. This first type of mutation just erases a letter during the process of copying.

ABC D EF → ABC EF

3.1.2 Change mutation. Run by a random-process one incoming letter is taken off during the process of copying and exchanged by a randomly selected other letter

ABC D EDG → ABC A EFG

3.1.3 Crossing-over-mutation. A subchain of randomly defined length is taken off the incoming chain and put back into the rewritten chain vice versa.

ABC DEFG HIJ → ABC GFED IJ

3.2 Tropism

As shown in various inquiries, dendrites grow in the realm of an inhibitory and/or excitatory gradientfield. Our first studies used a rotationsymmetric potentialfield affecting globally all those dendrites growing into this field. A force slightly changing the direction of growth towards the centre of the tropistic field is superimposed. The deviation depends on the strength of the gradientfield and the relative angle towards the centre.

3.3 Aging

Looking at age-dependent growth, it can be observed, that specific factors change their habits while systemtime passes on. Usually the whole system is affected by that (Bastiani et al. 1985; Campenot 1977). We have implemented this global factor in a way, that internal

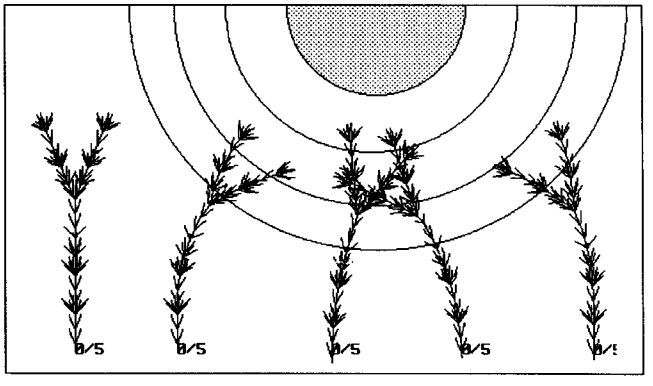

Fig. 7. Neurite trees growing in a tropistic field

values (e.g. stepwidth, angle, sprouting) of a cell are affected by an age-dependent random-process. In nature there are times, when sprouting of axons is tremendously high (e.g. in very young age), while the same process will happen less often when the whole set of neurons has become old.

3.4 Variances

Until now all processes, although they are of fractal nature are purely stochastic. The impressive result of this can be seen in Fig. 2a. The rewriting-process produces an object, which can obviously be added to the nonliving nature, for it could be perfectly described as a snowflake. The addition of any type of white noise or randomness to fractal processes (Mandelbrot et al. 1968) yields a totally different result. We have taken exactly the same genotype object in Fig. 2f and have overlaid a stochastic process, whereby after each move fo the "Turtle" a randomly chosen angle was added. The result has nothing to do with the genotype, for the deterministic effects overwhelm the ordered structures completely.

In defining growth as a stochastic process, overlapped by external factors (see Fig. 8) and a distinct measure of determinism uniqueness but reproducible classes can be found. Each object deriving from a given genotype has its individual phenotype, but within a well defined area of superimposed randomness, it clearly can be attached to its group.

Learning from that, we have enlarged the prior L-system by a stochastic factor, which externally can be set to distinct bandwidth. Whenever the character '**F**' standing for "move drawing unit into the given direction" appears it automatically will be followed by a randomly chosen angle within the given bandwidth.

To adapt objects to the given neurobiological facts, it is evident to add a naturalization-factor. By this we understand a random angle β from a given stochastic distribution, which is added to each given '*F*'. Before the process starts, the user has to define the distribution width of this angle.

e.g.: $\mathbf{F+F-FF \rightarrow F\beta + F\beta - F\beta F\beta}$

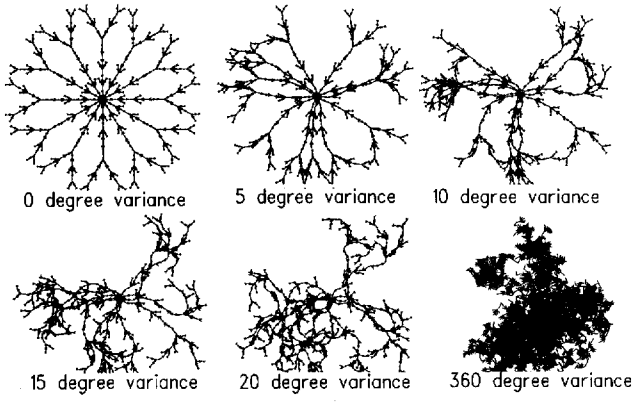

Fig. 8. Effects of naturalisation

4 Growing dendrites

Following the last picture, which was set up from 6 iterations, it is obvious, that the number of itertions cannot be identical with the steps of growth. For the purpose of receiving intermediate steps, we primarily have added the date of production. By this we mean the given iteration in which a specific letter is produced. Those letters, which can't be exchanged any more will keep this data, while those, which will be exchanged get lost anyway. Once the rewriting process has come to an end a specific counting-process takes place. Only specific letters (e.g. '*F*', '+') of a given date are used for this purpose. Starting with those letters from the 1. iteration the number of the specific letters from the given location towards the beginning is calculated (A). Once the maximum length is known (in our example it is 10), all numbers of a branch are shifted in a way, that the last given number of each branch will be $n_{\max}$ (B).

$$F[F[F]FFFFFF]FFF \rightarrow F\begin{array}{|l}|F\\F\\|FFF\end{array}FFFFFF \quad \text{(A)}$$

$$F[F[F]FFFFFF]FFF \rightarrow F\begin{array}{|l}\\F\\\\|FFF\end{array}FFFFFF \quad \text{(B)}$$

The reason for this procedure is, that in nature usually small branches are younger than bigger ones. Understanding the calculated number in terms of age-labels, a dynamic growth-process will only use those letters the age-label of which is smaller than a given number. Once this procedure is finished, the process will be repeated for all members of the following iteration, whereby the counting-process doesn't start at 0 but at $n_{\max}$ and therefore will end at $n2\max$. The age-labels will now lie beyond the highest age-label of the former generation. This setting of age-labels has to go on until all dedicated letters have received a label. At least the highest label will be $n^i_{\max}$. This is identical with the total number of growth-steps into which the whole growth-process can now be broken down. Beside this stepwise growth, this labeling technique is of high value for any sizing of these elements, for the label tells us the passed time since its creation within the currently growing dendritic tree.

5 Growth-cones

Using the idea of a local tropistic field, we can find within the realm of neurophysiological research (Brown 1991; Cruther 1986), that dendrites are able to find their way to their targets with the help of chemical markers and gradientfields. We have used this concept for another working hypothesis, which says, that each dendritic tree builds up a specific far reaching chemical attractorfield. The complete field is superimposed by local chemical attractor sources, put to define places within the tree.

Besides this, each neuron has sensors in each tip of its dendritic tree, which sense the gradientfield of a special type of attractor. Similar to the effects of tropism, these effectors force the whole object to grow towards the maximum gradient of the attractorfield.

As shown in neurobiological research, the path-finding of dendrites is given by chemical gradientfields, besides long-distance guidance. In our approach, we are only looking at such short-distant guidance in a way, that we postulate, that specific chemical gradient-field, given by the cell itself, as well as by other cells influences the growth of the very dendrite. To take this factor into account, we have added several independent layers of different chemical sources, which act according to Dales-principle on the various objects, we have put into the arena. Each chemical substrate has its own fade away time, so that the form and local strength of these fields depend on the ongoing time and the location where it was poured out. As these fields are nonlinear, they must be described numerically. Our working-hypothesis is, that each object owns attractor and effector elements. The effectors are defined in a way, that they pour out a quantity of chemical transmitter, once the desired letter in the given chain is activated. Because of its position and history, this happens only once at a distinct timing, which correlates to the general "clock" of growth. The attractors on the other hand sense the strength of the given chemical field, as well as its field gradient. Comparable to what had happened within the tropistic field, they try to shift along the field-vector. By that, the genotype of the dendritic tree is forced to change its direction incrementally.

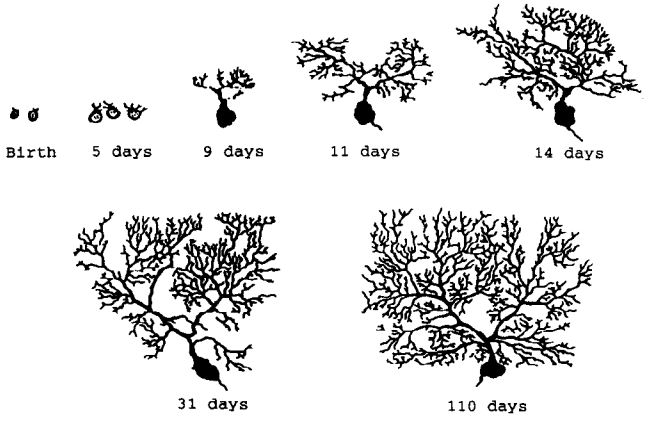

Fig. 9. Growth of the dendritic arbor of rat cerebellar Purkinje cells during the first several months of life. The neuron is shown for each age in postnatal days

Fig. 10. Growth of an artificial nervecell

6 Discussion

Rall discusses in his work done at an idealized neuron model mainly stem resistance simulations (Rall and Segev 1989). His work based on a deterministic setting within the neurite structure (Rall 1973), which puts the emphasis on signal conduction. Jeanpretre and Clark (1991) have presented a different model, where axonal growth comes from competitive growth of various neurites. In their model these neurites and their competition are described by different equations. They were able to show, that there are solutions. Bray (1979) used another model where dendritic growth and sprouting occurred randomly superimposed by an elastic force which shifts the direction of growth. A third model was presented by van Veen and Alt (1991), where randomly chosen outgrowth at the tips of the so called growth-cones produce a movement.

In using the rewriting-graph concept, deriving from Lindenmeyer's ideas (Does and Lindenmayer 1983; Eichhorst 1980; Herman and Lindenmayer 1975; Jürgensen and Lindenmayer 1987; Lindenmayer 1968a, b, 1974, 1975, 1979; Siromoney 1986), we able to create specific structures explicitly by setting up descriptive strings.

All of the other models are set up algebraicly, while our model derives from a setting similar to DNA coding. By that we set the DNA-sequences within the cell-nucleus, equal to the initial strings in our model. Although it would be too speculative to equate our rewriting model completely with the internal copying-processes within the cell, the effects given by using sequential strings are most impressive. Very easily effects occurring within the real DNA (e.g. mutations) can be understood in taking our model, where other models have much more problems with it. Another argument in using this model derives from the original Lindenmayer's idea in plant-biology (e.g. apex exchanged by branches, exchanged by internodes or segments, exchanged by leaves or buds, exchanged by flowers (see Prusinkiewics 1989 chap. 3).

Further, these algebraic models rely on random processes to an extent that can not be assumed to be present in real nervous systems.

An entirely different type of modelling neuritic growth was described by Pellionisz (1983, 1985, 1989), who used tensors in discussing the single dendritic trees and their interactions. These ideas are relevant to our approach insofar, as our aim in studying the growth-interactions between various types of nervecells might match quite closely with what was described by Pellionisz in a different way.

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