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Louis V. Quintas studied mathematics at Columbia University and The City University of New York. Since 1967 he has been a Professor of Mathematics at Pace University, New York, where he received The Kenan Outstanding Teacher Award in 1975 and the Dyson Society of Fellows Class of 1995 was named in his honor. He has written over a 100 research articles on functional equations, algebraic topology, combinatorial geometry, theoretical and algorithmic random graph theory, and on mathematical chemistry. He has also published textbooks on linear programming, statistics, and word processing. His teaching experience has exposed him to almost every topic in the undergraduate curriculum, with his favorites being discrete mathematics, probability, and statistics. He has co-chaired four international conferences on combinatorial mathematics and co-edited three of their proceedings. Since 1980 he has co-edited *Graph Theory Notes of New York*, which is published by The New York Academy of Sciences. He is a Fellow of the New York Academy of Science and has chaired its mathematics section. He is a regular presenter of his research at national and international conferences, workshops, and as a visitor to other universities. He has served twice as the chair of the mathematics department at Pace University and is active in the professional mathematical organizations AMS, MAA, and SIAM. He attibutes his love of mathematics to Howard Levi, Fred Supnick, and Alan J. Hoffman, the latter being his doctoral sponsor at The Graduate Center, CUNY.

Eric Wahl is a board certified obstetrician/gynecologist and clinical assistant professor at New York Medical College. He is a Fellow of the American College of Obstetricians and Gynecologists and has been in private practice in Manhattan since 1992. After graduating from St. George's University School of Medicine in 1988, Dr. Wahl completed his internship at the Catholic Medical Center of Brooklyn and Queens in New York. He then took a residency position at the Danbury Hospital and Yale University School of Medicine in 1990 during which he was awarded the distinction of Chief Resident from 1991-1992.

His special areas of interest include menopausal medicine, gynecological surgery and the study of angiogenesis in the microvasculature. Studies in the field of angiogenesis are very important not only in the development of normal vascular networks but also in understanding the pathophysiology of cancer and tumor growth. He is currently working on a graph theory model of the renal glomerular microvascular network and its development at Pace University. This represents an extension of his work as a master's student at the Columbia University School of Engineering and Applied Science in New York, and was published in Microvascular Research in 1983. Dr. Wahl began his graduate studies after completing a B.A. in Chemistry at the University of Utah in 1979.

RANDOM GRAPH PROCESS MODELS FOR ANGIOGENESIS

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1. Introduction

The two mechanisms of *angiogenesis* (blood vessel growth and formation) that have been most frequently observed are *sprouting* (budding) and *splitting* (intussusception). Observational studies in many in vivo models have been extensively reviewed [8][9].

The mathematical methods used to describe blood vessel growth, function, and vascular network patterns have used a variety of models such as fractal analysis of subcutaneous capillary growth in tumors and normal tissue [2], mass balance equations of angiogenetic tissue factor diffusion in corneal vessels [12], frequency distribution functions in a random branching scheme in mesenteric vessels [4], and graph theory to describe the topology (connectivity) of the renal glomerular capillary network [10][11][13].

Here we shall introduce models for angiogenesis based on random graph processes. A *Random Process* consists of a set of elements called *states* together with the probabilities of moving between any pair of states. These are called the *transition* *probabilities.* A *Random Graph Process* is a random process in which the states are graphs. These models will relate to sprouting, splitting and a third mechanism which we call *connecting* (anastomosing). The latter mechanism corresponds to sprouts joining to other parts of the capillary network. These mechanisms together with their graph theory equivalents are shown in Figure 1.

A vascular network of great interest is the *renal glomerulus,* a very small but intricate cluster of capillaries in the kidney. The renal glomerulus is viewed as a complex nonplanar network of capillaries, with a single feeding and a single (sometimes double) exiting vessel called the *afferent and efferent arterioles,* respectively. Observations in kidneys of the human fetus has shown that this complex glomerular network develops via the splitting mechanism from a single vessel (see [6]).

Our random graph process models may be compared with those renal glomerular networks that have been obtained by serial reconstruction of animal or human specimens. Models that use only sprouting and splitting are topologically planar. Models that incorporate the connecting mechanism generate nonplanar networks. Graph theory invariants involving distance and cycle structure, in addition to order, size, and planarity, will be used to compare networks generated by the random graph process models with those obtained experimentally.

This random graph process model of angiogenesis will allow us to investigate the topological properties of the renal glomerular network and it's development, and introduces for the first time a mathematical model to quantify angiogenesis in the vascular network.

2. Sprouting

The following algorithmic steps model the sprouting mechanism by defining a random graph process that has birooted labeled trees as states.

Step 0. Start with a birooted labeled directed edge (A, E).

For $s > 0$ proceed as follows.

Step s. Uniformly select an edge $\{x, y\}$ in the graph obtained at Step $(s-1)$, then replace the selected edge with a 3-star $St(3)$ by separately identifying vertices x and y with two vertices of degree 1 in $St(3)$ (*sprouting*).

Continue until a prespecified number N of steps have been executed.

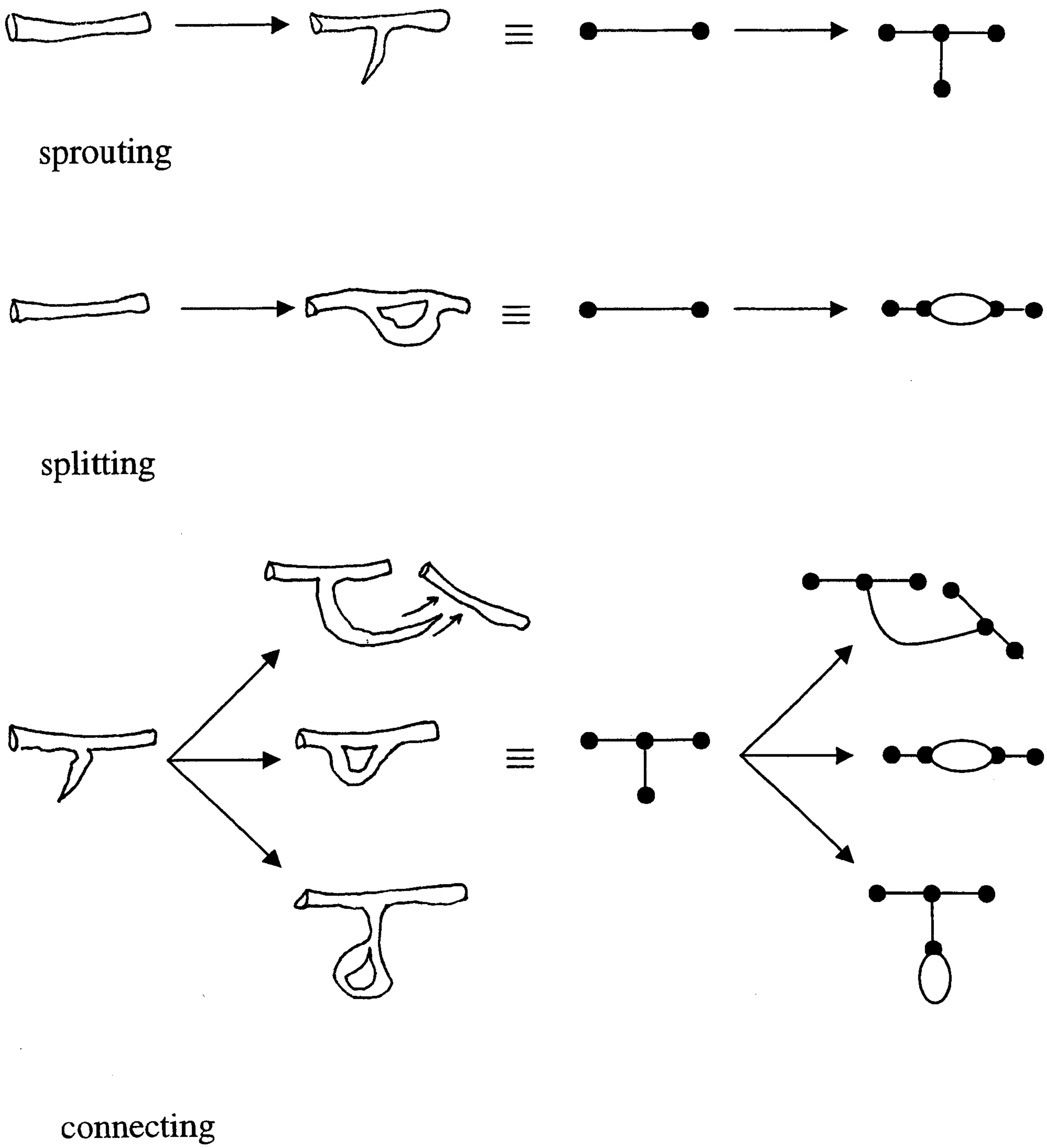

Figure 1. The graph theoretic equivalents of sprouting, splitting, and connecting

Immediate Observations

(1) The states obtained after three steps are shown in Figure 2. The vertices obtained in Step s are x_{2s+1} and x_{2s+2}. For simplicity in labeling, these vertices are denoted $2s+1$ and $2s+2$ in Figure 3, with 1 and 2 corresponding to A and E, respectively.

(2) The state at Step s is a birooted tree T_s having order $2s+2$ (and size $2s+1$) with roots A and E.

(3) T_s has s vertices of degree 3, and excluding the roots, s pendant vertices.

The states that are possible to obtain after s steps are said to be on *level s*.

(4) The *transition probability* from any tree T_{s-1} obtained at Step $(s-1)$ to any tree T_s on level s is the reciprocal of the number of edges of a tree on level $(s-1)$. All trees on the same level have the same size. Thus, the transition probability for $T_{s-1} \to T_s$ is $\frac{1}{1+2(s-1)} = \frac{1}{2s-1}$.

Theorem 2.1. *The probability of arriving at a state T_s in the Sprouting Model at Step s with $s \geq 1$ is*

$$P(T_s) = \frac{2^{s-1}(s-1)!}{(2s-1)!}.$$

Proof. Since the transition probability from any tree T_{s-1} obtained at Step $(s-1)$ to any tree T_s on level s is $\frac{1}{2s-1}$. The probability of arriving at T_s is the product of the probabilities from level 0 to level s, that is, $\frac{1}{1}\frac{1}{3}\frac{1}{5}\cdots\frac{1}{2s-1} = (\frac{1}{1}\frac{1}{3}\frac{1}{5}\cdots\frac{1}{2s-1})\frac{2}{2}\frac{4}{4}\frac{6}{6}\cdots\frac{(2s-2)}{(2s-2)} = \frac{2^{s-1}(s-1)!}{(2s-1)!}$. ■

Corollary 2.2. *The number of states on level s is $\frac{1}{P(T_s)} = \frac{(2s-1)!}{2^{s-1}(s-1)!}$.*

Proof. The states on level s are uniformly distributed. ■

The *eccentricity of vertex* x in T_s denoted $e(x)$ is the graph theoretic distance $d(x,z)$ to a vertex z in T_s farthest from x (see [3]). That is,

$$e(x) = \max\{d(x,y) : y \in T_s\}.$$

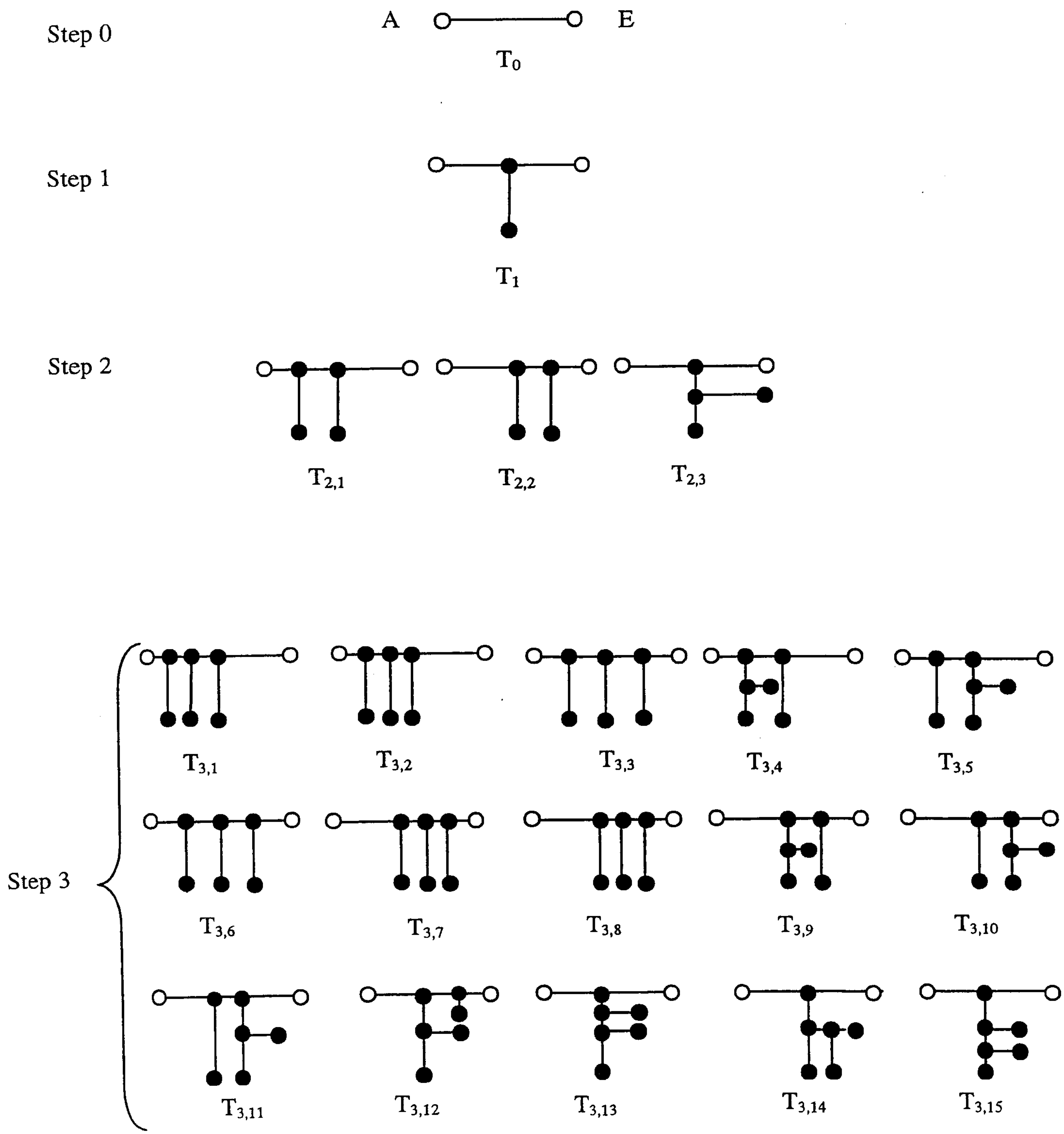

Figure 2. The states in the Sprouting Model for up to three steps

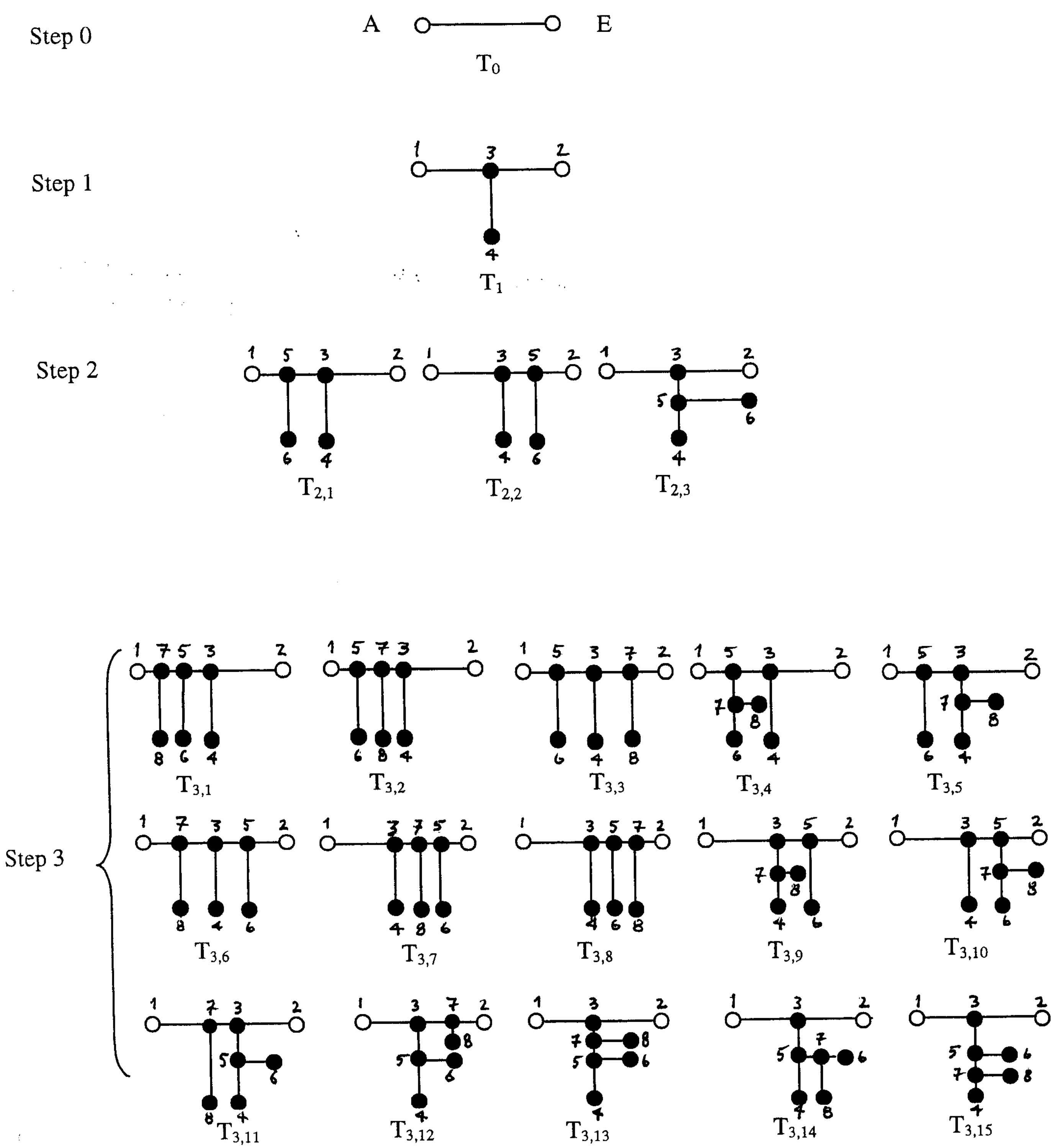

Figure 3. The vertex labeled states in the Sprouting Model for up to three steps

The *maximum root eccentricity of* T_s denoted Mre is defined

$$Mre = \max\{e(A), e(E)\}.$$

The *minimum root eccentricity of* T_s denoted mre is defined

$$mre = \min\{e(A), e(E)\}.$$

The *root distance* rd *of* T_s is the distance between the roots of T_s, that is,

$$rd = d(A, E).$$

Clearly, Mre, mre, and rd are random variables.

To illustrate the above concepts we have computed $e(A)$, $e(E)$, Mre, mre, and rd for each of the states T_s on level 3. The results of these computations are shown in Table 1.

T_s	$e(A)$	$e(E)$	Mre	mre	rd
$T_{3,1}$	4	4	4	4	4
$T_{3,2}$	4	4	4	4	4
$T_{3,3}$	4	4	4	4	4
$T_{3,4}$	3	4	4	3	3
$T_{3,5}$	4	3	4	3	3
$T_{3,6}$	4	4	4	4	4
$T_{3,7}$	4	4	4	4	4
$T_{3,8}$	4	4	4	4	4
$T_{3,9}$	3	4	4	3	3
$T_{3,10}$	4	3	4	3	3
$T_{3,11}$	4	3	4	3	3
$T_{3,12}$	3	4	4	3	3
$T_{3,13}$	4	4	4	4	2
$T_{3,14}$	4	4	4	4	2
$T_{3,15}$	4	4	4	4	2

Table 1. The values of $e(A)$, $e(E)$, Mre, mre, and rd for all of the states on level 3 in the Sprouting Model.

From Table 1 we obtain the following expectations and variances for the 3-step Sprouting Model. Using $Var(X) = E(X^2) - E^2(X)$, we have

$$E(e(A)) = E(e(E)) = 3(\frac{1}{5}) + 4(\frac{4}{5}) = \frac{19}{5} = 3\frac{4}{5},$$

$$Var(e(A)) = Var(e(E)) = 3^2(\frac{1}{5}) + 4^2(\frac{4}{5}) - (\frac{19}{5})^2 = \frac{4}{25} = .16,$$

$$E(Mre) = 4P(Mre = 4) = 4(\frac{15}{15}) = 4,$$

$$Var(Mre) = 0,$$

$$E(mre) = 3(\frac{6}{15}) + 4(\frac{9}{15}) = \frac{18}{5} = 3\frac{3}{5},$$

$$Var(mre) = 3^2(\frac{6}{15}) + 4^2(\frac{9}{15}) - (\frac{18}{5})^2 = \frac{6}{25} = .24,$$

and

$$E(rd) = 2(\frac{3}{15}) + 3(\frac{6}{15}) + 4(\frac{6}{15}) = \frac{16}{5} = 3\frac{1}{5},$$

$$Var(rd) = 2^2(\frac{3}{15}) + 3^2(\frac{6}{15}) + 4^2(\frac{6}{15}) - (\frac{16}{5})^2 = \frac{14}{25} = .56$$

Problem. After N steps, what is the expectation and variance for each of the random variables Mre, mre, and rd?

The expected value of rd after N steps is by definition

$$E(rd) = \sum_{i=1}^{N+1} iP(rd = i).$$

It is straight forward to determine $P(rd = i)$ at Step N when $i = 1, 2$, and $N + 1$. Namely,

$$P(rd = 1) = 1 \quad (N = 0),$$

$$P(rd = 1) = 0 \quad (N \geq 1),$$

$$P(rd = 2) = 0 \quad (N = 0),$$

$$P(rd = 2) = 1\frac{1}{3}\frac{3}{5}\frac{5}{7}\frac{7}{9}\cdots\frac{2N-3}{2N-1} = \frac{1}{2N-1} \quad (N \geq 2),$$

and

$$P(rd = N+1) = 1\frac{2}{3}\frac{3}{5}\frac{4}{7}\frac{5}{9}\cdots\frac{N}{2N-1} = \frac{N!2^{N-1}(N-1)!}{(2N-1)!} \quad (N \geq 2).$$

However, it is more complex to compute $P(rd = i)$ combinatorially when $3 \leq i \leq N$, since in these cases there are many variations on how a tree can arrive at level N and have $rd = i$.

In Figure 4 we show the transition digraph for the Sprouting Model for up to three steps with the states gathered together into isomorphism classes, each of which is represented with an unlabeled birooted tree of order 8.

3. Splitting

For the splitting mechanism, the following steps algorithmically define a random graph process model that has birooted labeled multigraphs as states.

Step 0. Start with a birooted labeled directed edge (A, E).

For $s > 0$ proceed as follows.

Step s. Let H denote a 2-cycle having a pendant edge at each of its two vertices. Next uniformly select an edge $\{x, y\}$ in the graph obtained at Step $(s-1)$. Then, replace the selected edge with H, by identifying vertices x and y, respectively, with the vertices of degree 1 in H (*splitting*).

Continue until a prespecified number N of steps have been executed.

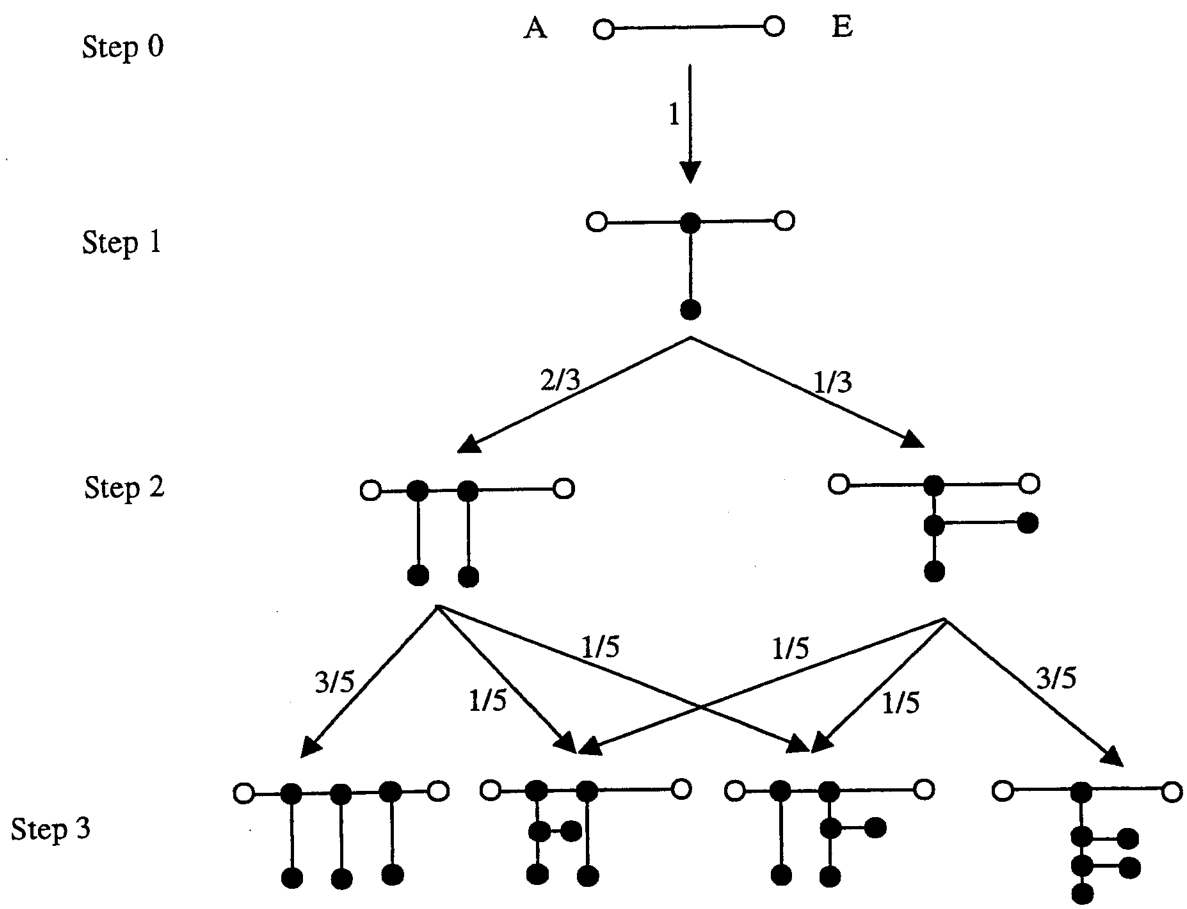

Figure 4. The transition digraph for the Sprouting Model for up to three steps with the states gathered together into isomorphism classes.

Immediate Observations with respect to the Splitting Model

(1) The states obtained after three steps are shown in Figure 5. Although not shown in this figure, it is understood that the vertices obtained in Step s are x_{2s+1} and x_{2s+2}. For simplicity in labeling, these vertices can be denoted $2s+1$ and $2s+2$, with A and E corresponding to 1 and 2, respectively. Also note that due to the scale of this figure A and E are denoted by dots, rather than open circles, and all other vertices simply as branch points.

(2) The state at Step s is a birooted multigraph G_s having order $2+2s$, size $1+3s$, and with roots A and E the only vertices of degree 1.

(3) G_s has $2s$ vertices of degree 3 and s independent cycles. The latter is also known as the *cycle rank* β of G_s and is obtained in general for any graph by the equation $\beta = t - n + c$, where t, n, and c are the size, order, and number of components of the graph.

(4) The transition probability from any graph G_{s-1} obtained at Step $(s-1)$ to any graph G_s on level s is the reciprocal of the number of edges of a graph on level $(s-1)$. Namely, the transition probability for $G_{s-1} \to G_s$ is $\frac{1}{1+3(s-1)} = \frac{1}{3s-2}$.

Theorem 3.1. *The probability of arriving at a state G_s in the Splitting Model at Step s with $s \geq 1$ is*

$$P(G_s) = \frac{1}{1}\frac{1}{4}\frac{1}{7}\frac{1}{10}\frac{1}{13}\cdots\frac{1}{3s-2}.$$

Proof. Since the transition probability from any graph G_{s-1} obtained at Step $(s-1)$ to any graph G_s on level s is $\frac{1}{3s-2}$. The probability of arriving at T_s is the product of the probabilities from level 0 to level s, that is, $\frac{1}{1}\frac{1}{4}\frac{1}{7}\frac{1}{10}\cdots\frac{1}{3s-2}$. ■

Corollary 3.2. *The number of states on level s is* $\frac{1}{P(G_s)} = 1\cdot 4\cdot 7\cdot 10\cdot\cdots\cdot(3s-2)$.

Proof. The states on level s are uniformly distributed. ■

Problem. Write $\frac{1}{P(G_s)} = 1\cdot 4\cdot 7\cdot 10\cdot\cdots\cdot(3s-2)$ in closed form.

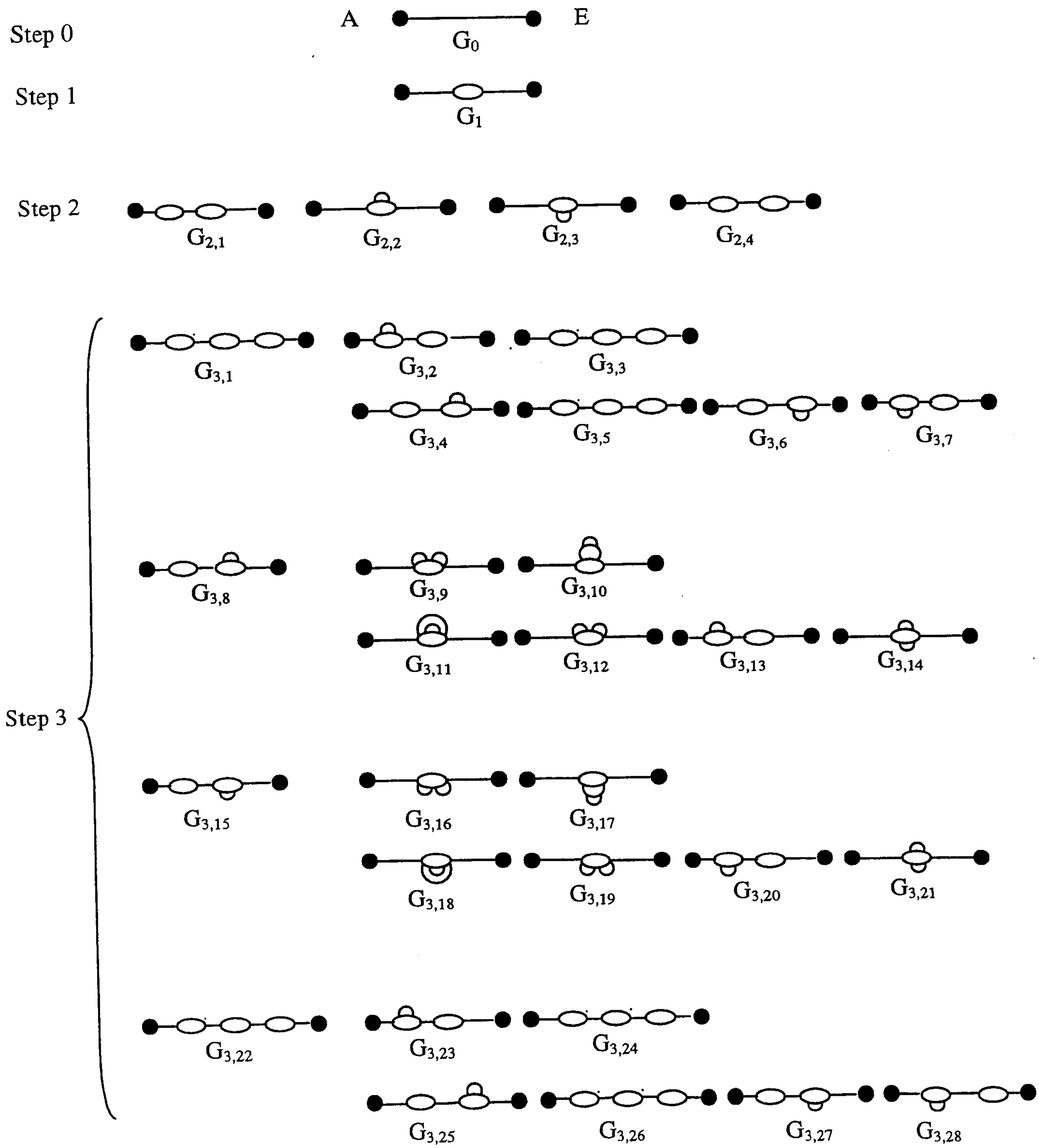

Figure 5. The states in the Splitting Model for up to three steps.

In addition to the random variables $e(A)$, $e(E)$, Mre, mre, and rd defined in Section 2, random variables involving the cycle structure of G_s are of interest. For example, we define

$$X_j = \text{number of cycles of size } j$$

and

$$X = \text{number of cycles.}$$

To illustrate the above concepts we have computed $e(A)$, $e(E)$, Mre, mre, rd, X_j, and X for all of the states on level 3. The result of these computations, for $e(A)$, $e(E)$, Mre, mre, and rd, are shown in Table 2 and for X_j and X in Table 3.

From Table 2 we obtain the following expectations and variances for the 3-step Splitting Model.

$$E(e(A)) = E(e(E)) = 4(\frac{8}{28}) + 5(\frac{14}{28}) + 7(\frac{6}{28}) = \frac{36}{7} = 5\frac{1}{7},$$

$$Var(e(A)) = Var(e(E)) = 4^2(\frac{8}{28}) + 5^2(\frac{14}{28}) + 7^2(\frac{6}{28}) - (\frac{36}{7})^2 = \frac{55}{49} = 1.1224,$$

$$E(Mre) = E(mre) = 4(\frac{8}{28}) + 5(\frac{14}{28}) + 7(\frac{6}{28}) = \frac{36}{7} = 5\frac{1}{7},$$

$$Var(Mre) = Var(mre) = 16(\frac{8}{28}) + 25(\frac{14}{28}) + 49(\frac{6}{28}) - (\frac{36}{7})^2 = \frac{55}{49} = 1.1224,$$

and

$$E(rd) = 3(\frac{8}{28}) + 5(\frac{14}{28}) + 7(\frac{6}{28}) = \frac{34}{28} = 4\frac{6}{7}$$

$$Var(rd) = 9(\frac{8}{28}) + 25(\frac{14}{28}) + 49(\frac{6}{28}) - (\frac{34}{7})^2 = \frac{193}{98} = 1.9694$$

Problem. For the N-step Splitting Model, what is the expectation and variance for each of the random variables $e(A)$, $e(E)$, Mre, mre, and rd?

G_s	$e(A)$	$e(E)$	Mre	mre	rd
$G_{3,1}$	7	7	7	7	7
$G_{3,2}$	5	5	5	5	5
$G_{3,3}$	7	7	7	7	7
$G_{3,4}$	5	5	5	5	5
$G_{3,5}$	7	7	7	7	7
$G_{3,6}$	5	5	5	5	5
$G_{3,7}$	5	5	5	5	5
$G_{3,8}$	5	5	5	5	5
$G_{3,9}$	4	4	4	4	3
$G_{3,10}$	4	4	4	4	3
$G_{3,11}$	4	4	4	4	3
$G_{3,12}$	4	4	4	4	3
$G_{3,13}$	5	5	5	5	5
$G_{3,14}$	5	5	5	5	5
$G_{3,15}$	5	5	5	5	5
$G_{3,16}$	4	4	4	4	3
$G_{3,17}$	4	4	4	4	3
$G_{3,18}$	4	4	4	4	3
$G_{3,19}$	4	4	4	4	3
$G_{3,20}$	5	5	5	5	5
$G_{3,21}$	5	5	5	5	5
$G_{3,22}$	7	7	7	7	7
$G_{3,23}$	5	5	5	5	5
$G_{3,24}$	7	7	7	7	7
$G_{3,25}$	5	5	5	5	5
$G_{3,26}$	7	7	7	7	7
$G_{3,27}$	5	5	5	5	5
$G_{3,28}$	5	5	5	5	5

Table 2. The values of $e(A)$, $e(E)$, Mre, mre, and rd for all of the states on level 3 in the Splitting Model.

From Table 3 we obtain the following expectations and variances for the cycle structure in the 3-step Splitting Model.

$$E(X_2) = 1(\frac{4}{28}) + 2(\frac{18}{28}) + 3(\frac{6}{28}) = \frac{29}{14} = 2\frac{1}{14},$$

$$Var(X_2) = 1^2(\frac{4}{28}) + 2^2(\frac{18}{28}) + 3^2(\frac{6}{28}) - (\frac{29}{14})^2 = \frac{69}{196} = .3520,$$

$$E(X_4) = 0(\frac{12}{28}) + 2(\frac{12}{28}) + 3(\frac{4}{28}) = \frac{18}{14} = 1\frac{2}{7},$$

$$Var(X_4) = 0^2(\frac{12}{28}) + 2^2(\frac{12}{28}) + 3^2(\frac{4}{28}) - (\frac{18}{14})^2 = \frac{66}{49} = 1.3469,$$

$$E(X_6) = 0(\frac{18}{28}) + 2(\frac{4}{28}) + 4(\frac{6}{28}) = \frac{16}{14} = 1\frac{1}{7},$$

$$Var(X_6) = 0^2(\frac{18}{28}) + 2^2(\frac{4}{28}) + 4^2(\frac{6}{28}) - (\frac{16}{14})^2 = \frac{132}{49} = 2.6939,$$

and

$$E(X) = 3(\frac{6}{28}) + 4(\frac{12}{28}) + 6(\frac{10}{28}) = \frac{63}{14} = 4\frac{1}{2},$$

$$Var(X) = 3^2(\frac{6}{28}) + 4^2(\frac{12}{28}) + 6^2(\frac{10}{28}) - (\frac{63}{14})^2 = \frac{263}{196} = 1.3418$$

Recall that $\beta = s$ on level s in this model, so that all multigraphs on level 3 have 3 independent cycles.

Problem. For the N-step Splitting Model, what is the expectation and variance for each of the random variables X_j and X?

G_s	X_2	X_4	X_6		X
$G_{3,1}$	3	0	0	=	3
$G_{3,2}$	2	2	0	=	4
$G_{3,3}$	3	0	0	=	3
$G_{3,4}$	2	2	0	=	4
$G_{3,5}$	3	0	0	=	3
$G_{3,6}$	2	2	0	=	4
$G_{3,7}$	2	2	0	=	4
$G_{3,8}$	2	2	0	=	4
$G_{3,9}$	2	0	4	=	6
$G_{3,10}$	1	3	2	=	6
$G_{3,11}$	1	3	2	=	6
$G_{3,12}$	2	0	4	=	6
$G_{3,13}$	2	2	0	=	4
$G_{3,14}$	2	0	4	=	6
$G_{3,15}$	2	2	0	=	4
$G_{3,16}$	2	0	0	=	2
$G_{3,17}$	1	3	2	=	6
$G_{3,18}$	1	3	2	=	6
$G_{3,19}$	2	0	4	=	6
$G_{3,20}$	2	2	0	=	4
$G_{3,21}$	2	0	4	=	6
$G_{3,22}$	3	0	0	=	3
$G_{3,23}$	2	2	0	=	4
$G_{3,24}$	3	0	0	=	3
$G_{3,25}$	2	2	0	=	4
$G_{3,26}$	3	0	0	=	3
$G_{3,27}$	2	2	0	=	4
$G_{3,28}$	2	2	0	=	4

Table 3. The values of X_j and X for all of the states on level 3 in the Splitting Model.

In Figure 6 we show the transition digraph for the Splitting Model for up to three steps with the states gathered together into isomorphism classes, each of which is represented with an unlabeled birooted multigraph of order 8.

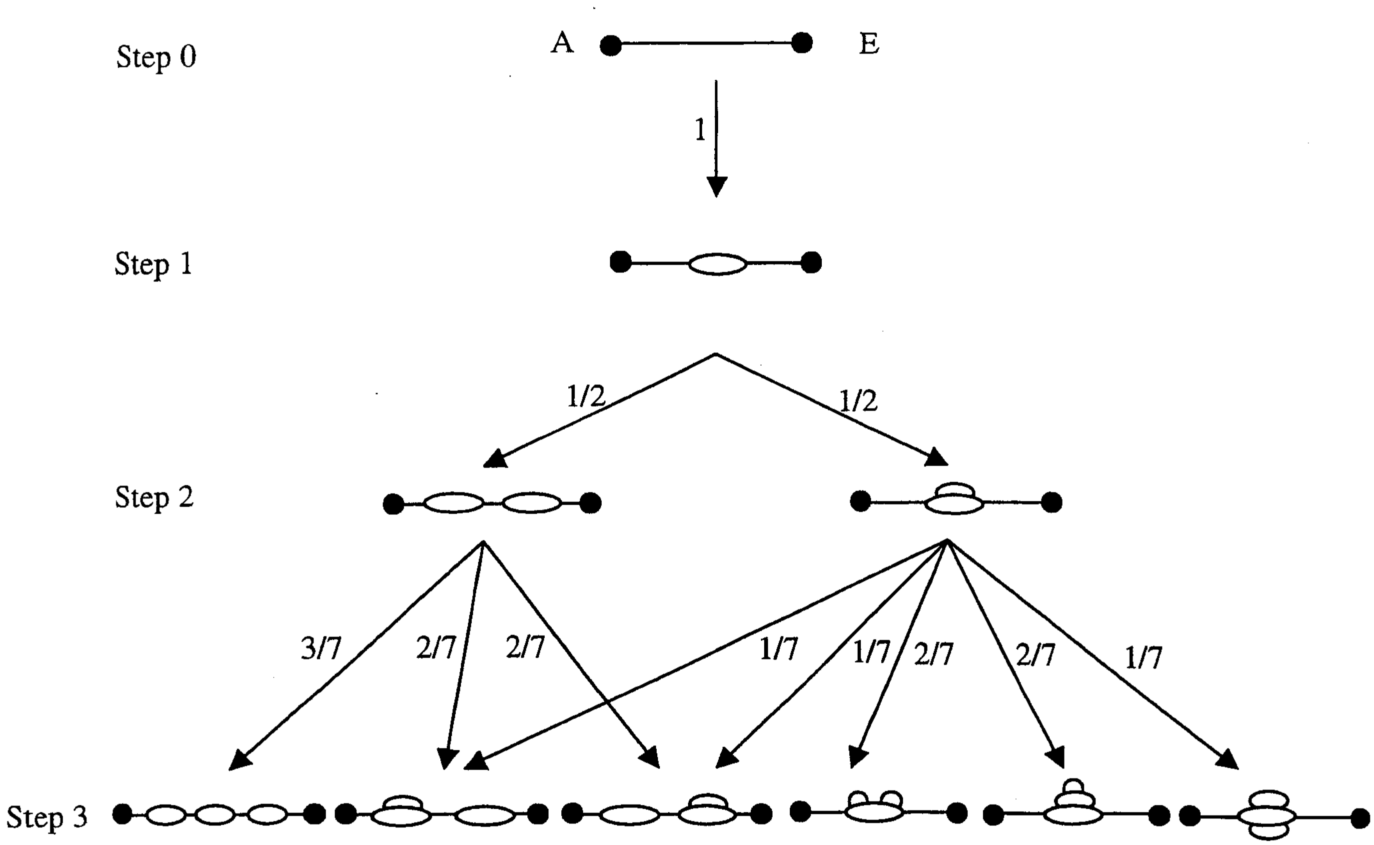

Figure 6. The transition digraph for the Splitting Model for up to three steps with the states gathered together into isomorphism classes.

4. Sprouting and Splitting

For the sprouting and splitting mechanisms, the following steps define a random graph process model that has birooted labeled multigraphs as states.

Step 0. Start with a birooted labeled directed edge (A, E).

For $s > 0$ proceed as follows.

Step s. Uniformly select an edge $\{x, y\}$ in the graph obtained at Step $(s-1)$, then with equal probability replace $\{x, y\}$ either by

sprouting at that edge (see Section 2)

or

splitting the selected edge (see Section 3).

Continue until a prespecified number N of steps have been executed.

Immediate Observations.

(1) In Figure 7*a* we show the (labeled) states obtained in the Sprouting and Splitting Model after two steps. Also shown, in Figure 7*b*, is the transition digraph for these steps with the states gathered together into isomorphism classes each represented by an unlabeled graph of order 6.

Problem. What is the number of labeled (unlabeled) birooted multigraphs obtained after s steps in the Sprouting and Splitting Model.

(2) The *transition probability* from a labeled graph G_{s-1} obtained at Step $(s-1)$ to a graph G_s on level s is the reciprocal of twice the number of edges of G_{s-1} and the number of labeled graphs that can be obtained from G_{s-1} is twice the number of its edges. This is so because each edge in G_{s-1} can either sprout or be split.

Problem. Study the random variables defined in Sections 2 and 3, namely, $e(A)$, $e(E)$, Mre, mre, rd, X_j, and X for the Sprouting and Splitting Model.

As an illustration we shall determine values for these random variables for the Sprouting and Splitting Model for the states on level 2. These are shown in Table 4.

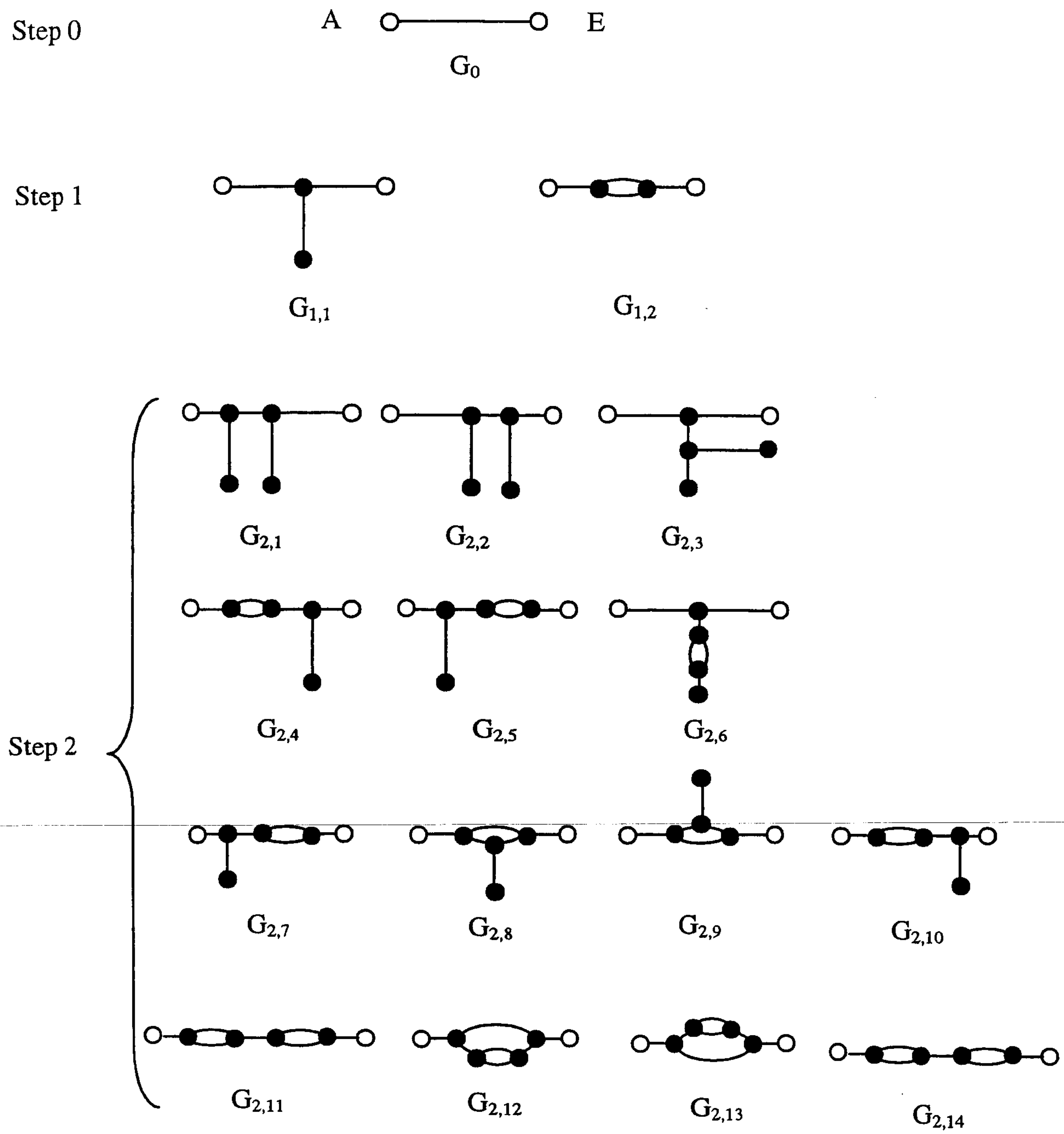

Figure 7a. The states obtained in the Sprouting and Splitting Model for up to two steps.

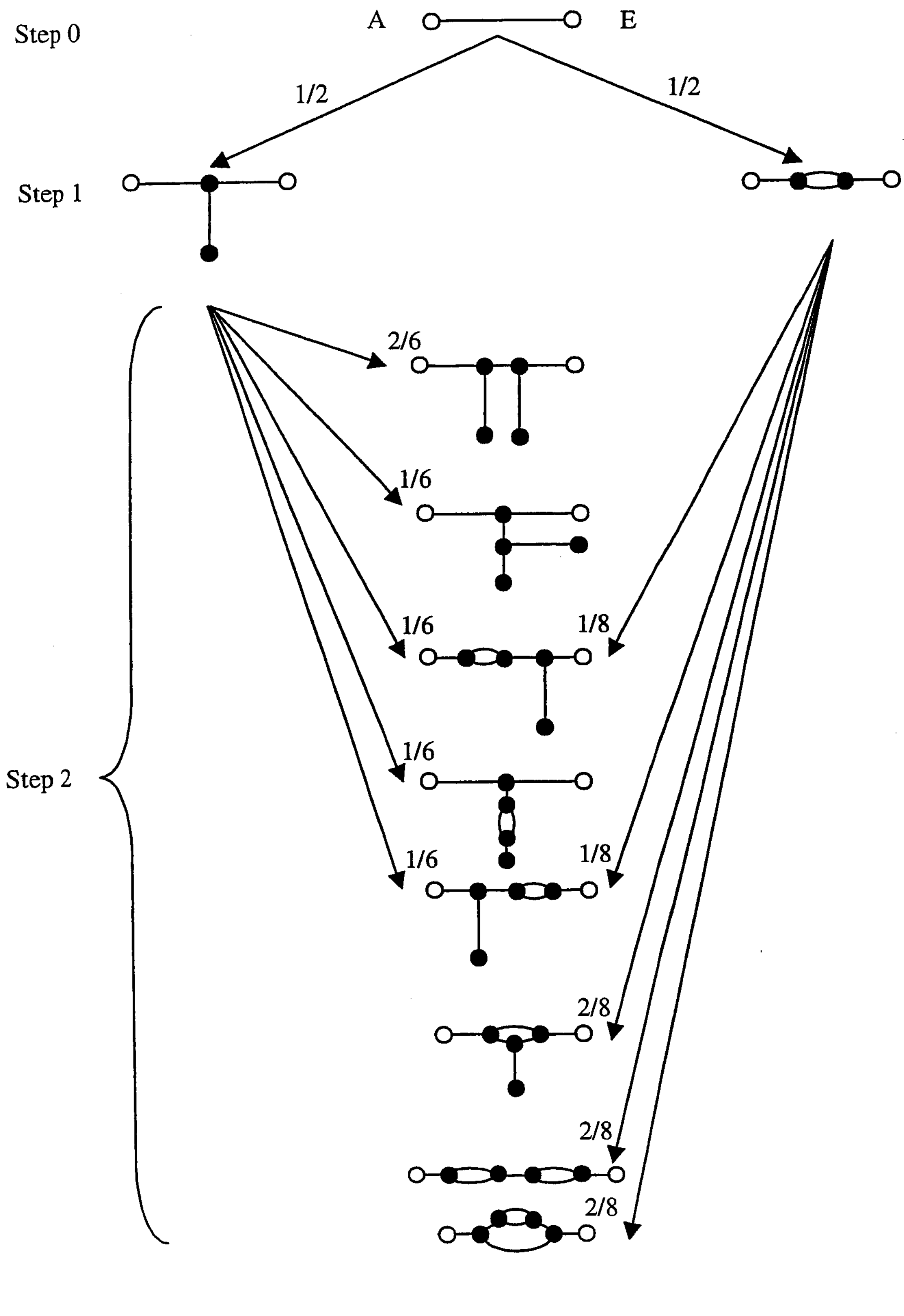

Figure 7b. The transition digraph for the Sprouting and Splitting Model for up to two steps with the states gathered together into isomorphism classes.

	$e(A)$	$e(E)$	Mre	mre	rd	X_2	X_3	X_4		X
$G_{2,1}$	3	3	3	3	3	0	0	0	=	0
$G_{2,2}$	3	3	3	3	3	0	0	0	=	0
$G_{2,3}$	3	3	3	3	2	0	0	0	=	0
$G_{2,4}$	4	4	4	4	4	1	0	0	=	1
$G_{2,5}$	4	4	4	4	4	1	0	0	=	1
$G_{2,6}$	4	4	4	4	2	1	0	0	=	1
$G_{2,7}$	4	4	4	4	4	1	0	0	=	1
$G_{2,8}$	3	3	3	3	3	0	1	0	=	1
$G_{2,9}$	3	3	3	3	3	0	1	0	=	1
$G_{2,10}$	4	4	4	4	4	1	0	0	=	1
$G_{2,11}$	5	5	5	5	5	2	0	0	=	2
$G_{2,12}$	3	3	3	3	3	1	0	2	=	3
$G_{2,13}$	3	3	3	3	3	1	0	2	=	3
$G_{2,14}$	5	5	5	5	5	2	0	0	=	2

Table 4. The values of $e(A), e(E), Mre, mre, rd, X_j$ and X for all of the states on level 2 in the Sprouting and Splitting Model.

Note that the distribution on level 2 is not uniform and that $E(e(A)) = E(e(E)) = E(Mre) = E(mre)$. Referring to Figure 7*b* we obtain the following expectations and variances.

$$\begin{aligned} E(e(A)) &= 3(\frac{4}{8}) + 4(\frac{3}{8}) + 5(\frac{1}{8}) = \frac{29}{8} = 3\frac{5}{8}, \\ Var(e(A)) &= 9(\frac{4}{8}) + 16(\frac{3}{8}) + 25(\frac{1}{8}) - (\frac{29}{8})^2 = \frac{31}{64} = .4844, \end{aligned}$$

$$\begin{aligned} E(rd) &= 2(\frac{4}{24}) + 3(\frac{10}{24}) + 4(\frac{7}{24}) + 5(\frac{3}{24}) = \frac{27}{8} = 3\frac{3}{8}, \\ Var(rd) &= 4(\frac{4}{24}) + 9(\frac{10}{24}) + 16(\frac{7}{24}) + 25(\frac{3}{24}) - (\frac{27}{8})^2 = .8177, \\ E(X_2) &= 0(\frac{18}{48}) + 1(\frac{24}{48}) + 2(\frac{6}{48}) = \frac{36}{48} = \frac{3}{4}, \\ Var(X_2) &= 0 + 1(\frac{24}{48}) + 4(\frac{6}{48}) - (\frac{3}{4})^2 = \frac{7}{16} = .4375, \end{aligned}$$

$$\begin{aligned} E(X_3) &= 1(\frac{1}{8}) = \frac{1}{8}, \\ Var(X_3) &= 1(\frac{1}{8}) - \frac{1}{64} = \frac{7}{64} = .1094, \end{aligned}$$

$$\begin{aligned} E(X_4) &= 2(\frac{1}{8}) = \frac{1}{4}, \\ Var(X_4) &= 4(\frac{1}{8}) - \frac{1}{16} = \frac{7}{16} = .4375, \end{aligned}$$

and

$$\begin{aligned} E(X) &= 0(\frac{12}{48}) + 1(\frac{24}{48}) + 2(\frac{6}{48}) + 3(\frac{6}{48}) = \frac{9}{8} = 1\frac{1}{8}, \\ Var(X) &= 0(\frac{12}{48}) + 1(\frac{24}{48}) + 4(\frac{6}{48}) + 9(\frac{6}{48}) - (\frac{9}{8})^2 = \frac{102}{48} - \frac{81}{64} = .8594 \end{aligned}$$

Problem. After N steps, what is the expectation and variance for each of the random variables $e(A), e(E), Mre, mre$, and X for the Sprouting and Splitting Model?

5. Sprouting and Connecting

First we define a random graph process which provides a model for the sprouting and connecting mechanisms. Here the states are birooted labeled multigraphs with loops.

Step 0. Start with a birooted directed edge (A, E).

For $s > 0$, proceed as follows.

Step s. Uniformly select either an edge or a pendant vertex (other than A or E) in the state obtained in Step $(s-1)$.

(i) If an edge is selected, apply the sprouting transformation at that edge (see Section 2).

(ii) If a pendant vertex is selected, then apply the *connecting transformation* whose graph theoretic equivalence is represented by a pendant vertex being identified with an interior point of an edge (see Figure 1).

Continue until a specified number N of steps have been executed.

Immediate Observations

(1) For $s > 0$,the number of possible transformations of a graph with t edges and x pendant vertices other than A and E in the Sprouting and Connecting Model is equal to $t + xt$. This is clear since each allowable pendant vertex can be connected with any edge of the graph.

(2) In Figure 8 we show the transition digraph for the Sprouting and Connecting Model for up to three steps with the states gathered together into isomorphism classes. The graphs on level 3 are the eleven graphs drawn in a column and although not labeled in Figure 8 will be referred to as G_i $(i = 1, 2, \ldots, 11)$ in what follows.

From Figure 8 we can obtain the values of the probabilities of the states on level 3. The values of the random variables $e(A), e(E), Mre, mre, X_j$, and X for the Sprouting and Connecting Model for these states can also be read off from Figure 8. These values are shown in Table 5.

	$e(A)$	$e(E)$	Mre	mre	rd	X_1	X_2	X_3		X
G_1	4	4	4	4	4	0	0	0	=	0
G_2	3	4	4	3	3	0	0	0	=	0
G_3	4	3	4	3	3	0	0	0	=	0
G_4	4	4	4	4	4	0	1	0	=	1
G_5	3	3	3	3	3	1	0	0	=	1
G_6	3	3	3	3	3	0	0	1	=	1
G_7	4	4	4	4	4	0	1	0	=	1
G_8	3	3	3	3	3	1	0	0	=	1
G_9	4	4	4	4	2	0	0	0	=	0
G_{10}	4	4	4	4	2	0	1	0	=	1
G_{11}	3	3	3	3	2	1	0	0	=	1

Table 5. The values of $e(A), e(E), Mre, mre, rd$, X_j and X for all of the states on level 3 in the Sprouting and Connecting Model.

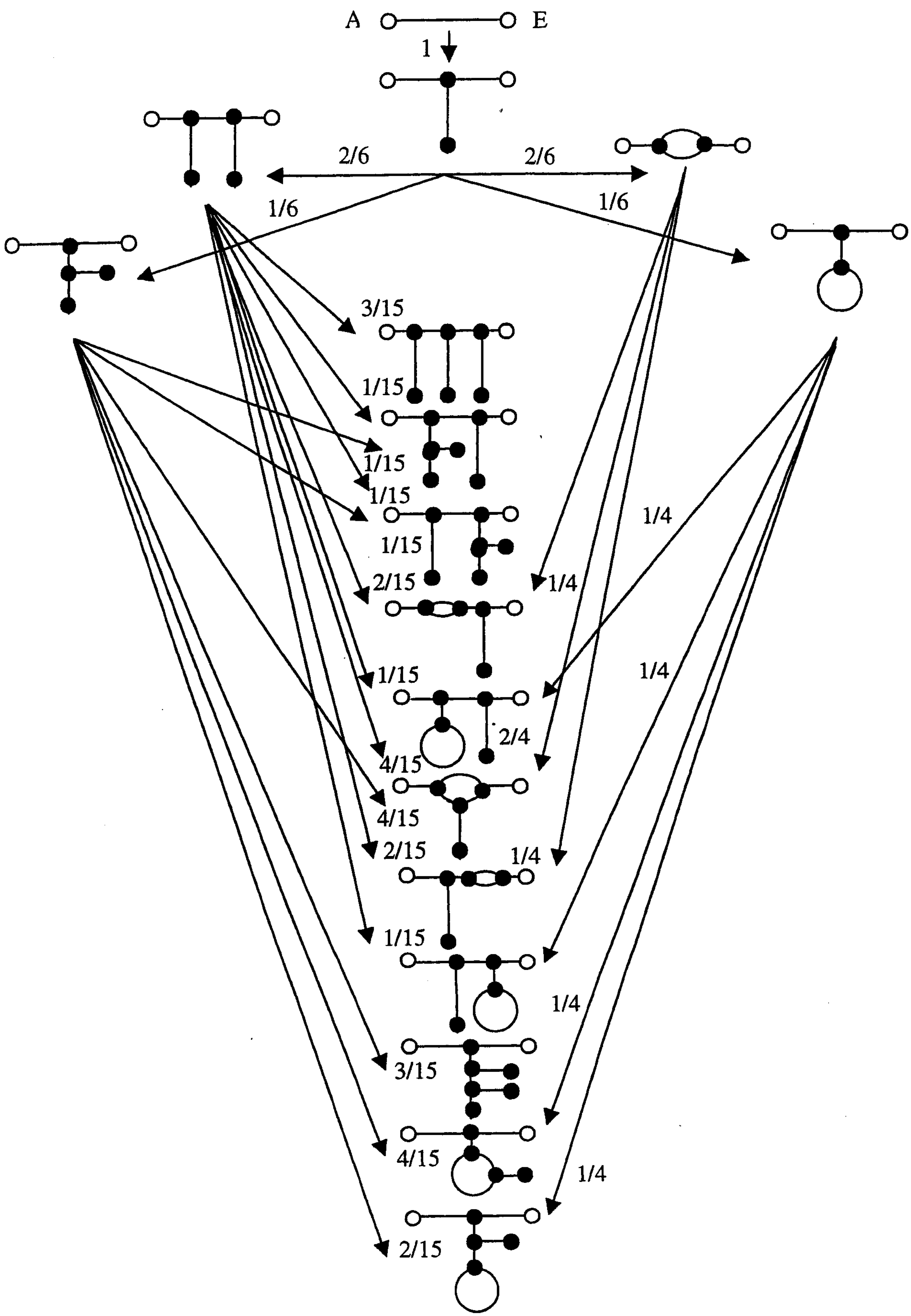

Figure 8. The transition digraph for the Sprouting and Connecting Model for up to three steps with the states gathered together into isomorphism classes.

The probabilities for the states of the Sprouting and Connecting Model obtained after 3 steps are as follows.

$$P(G_1) = \frac{1}{15}, \quad P(G_2) = \frac{1}{45} + \frac{1}{90} = \frac{1}{30}, \quad P(G_3) = \frac{1}{45} + \frac{1}{90} = \frac{1}{30},$$

$$P(G_4) = \frac{2}{45} + \frac{1}{12} = \frac{23}{180}, \quad P(G_5) = \frac{1}{45} + \frac{1}{24} = \frac{23}{360},$$

$$P(G_6) = \frac{1}{3}(\frac{4}{15}) + \frac{1}{6}(\frac{4}{15}) + \frac{1}{6} = \frac{3}{10}, \quad P(G_7) = \frac{1}{3}(\frac{2}{15}) + \frac{1}{3}(\frac{1}{4}) = \frac{23}{180},$$

$$P(G_8) = \frac{1}{45} + \frac{1}{24} = \frac{23}{360}, \quad P(G_9) = \frac{1}{30},$$

$$P(G_{10}) = \frac{2}{45} + \frac{1}{24} = \frac{31}{360}, \quad P(G_{11}) = \frac{1}{45} + \frac{1}{24} = \frac{23}{360}$$

From the values given in Table 5 and the above probabilities we obtain the following expectations and variances.

$$E(e(A)) = 3\frac{19}{40}, \quad Var(e(A)) = \frac{399}{1600} = .2494,$$

$$E(e(E)) = 3\frac{19}{40}, \quad Var(e(E)) = \frac{399}{1600} = .2494,$$

$$E(Mre) = 3\frac{61}{120}, \quad Var(Mre) = \frac{3599}{14400} = .2499,$$

$$E(mre) = 3\frac{53}{120}, \quad Var(mre) = \frac{3551}{14400} = .2466,$$

$$E(rd) = 3\frac{5}{36}, \quad Var(rd) = \frac{3151}{6480} = .4863,$$

$$E(rd) = 3\frac{5}{36}, \quad Var(rd) = \frac{3151}{6480} = .4863,$$

$$E(X_1) = \frac{69}{360}, \qquad Var(X_1) = \frac{2231}{14400} = .1549,$$

$$E(X_2) = \frac{23}{180} + \frac{23}{180} + \frac{31}{360} = \frac{41}{120}, \qquad Var(X_2) = \frac{41}{120} - (\frac{41}{120})^2 = \frac{3239}{14400} = .2249,$$

$$E(X_3) = \frac{3}{10}, \qquad Var(X_3) = \frac{3}{10} - (\frac{3}{10})^2 = \frac{21}{100} = .2100,$$

and

$$E(X) = \frac{5}{6}, \qquad Var(X) = \frac{5}{36} = .1389$$

6. Sprouting, Splitting, and Connecting

In this section we shall examine a process that permits the mechanisms of sprouting, splitting, and connecting. From Figure 1 and previous sections we know the graph theoretic equivalents of these mechanisms.

For the sprouting, splitting, and connecting mechanisms the following steps define a random graph process having birooted labeled multigraphs with loops as states.

Step 0. Start with a birooted labeled directed edge (A, E).

For $s > 0$ proceed as follows.

Step s. Uniformly select either an edge or a pendant vertex (other than A or E) in the state obtained in Step $(s-1)$.

(i) if an edge is selected,
then with equal probability replace that edge either by
sprouting at that edge (see Section 2)
or by
splitting the selected edge (see Section 3).

(ii) if a pendant vertex is selected, then apply the connecting transformation to that vertex (see Section 5).

Continue until a specified number N of steps have been executed.

Immediate Observations.

(1) For $s > 0$, let n, t, and x denote the number of vertices, edges, and pendant vertices other than the roots, respectively, then the number of possible transformations for a given graph is as follows.

For sprouting there are t edges, for splitting there are t edges, and for connecting there are xt possibilities. Thus, the number of possible transformations of a given graph is

$$2t + xt = t(2 + x).$$

(2) Note that the number of graphs generated at each level in the Sprouting, Splitting, and Connecting Model is much larger than that for the model that employs just sprouting and connecting. Thus, figures become cumbersome. Consequently, for this model and for higher levels of the preceding models a computer aided study will be used in future studies.

7. Properties of some vascular networks

Vascular networks of various complexities have been found in both humans and animals. Examples of these networks can be seen in the embryonic yolk sac [9], abdominal mesentery [4], human cornea [12], and the renal glomerulus [6].

These networks are very important because they represent in part the transition between arterial and venous systems and the location of the greatest surface area for oxygen and electrolyte exchange. In the case of the renal glomerulus, the ultrafiltration unit of the kidney, its function is fundamental to maintenance of blood pressure.

Dynamically, vascular networks can be represented by conduits that have Euclidean dimension (length, diameter, circumference, etc.) and fluid transport properties (flow, diffusion, etc.). Topologically, the vascular networks are described in terms of graphs (vertices, edges, cycles, planarity, etc.).

Mass balance equations of flow has been used to describe angiogenic tissue factor diffusion in corneal vessels [12]. Stereogenesis (computer aided reconstruction of in vivo specimens) has been frequently employed to measure the dimensions of blood vessels [7][10]. More recently, fractal analysis has provided a way of describing the branching pattern of vascular trees [2].

This article attempts to expand the concept of using a graph theory model to describe not only the branching pattern of vascular networks but also to provide a growth model of development. Although this model does not provide information about a network's Euclidean properties, it has the potential of providing information about network flow.

The basic invariants that make up a graph are the number of vertices and edges. Vertex degrees, distance properties, and cycle structure further characterize graphs in the case of vascular networks. Correlations between graph invariants and the vascular network has been previously demonstrated [10][13]. Edges and vertices represent blood vessels and their branch points respectively. In the case of the renal glomerulus, the fewest number of vessels from afferent arteriole to efferent arteriole is represented in this study by the graph invariant root distance (rd). Furthermore, the previously described "lobular pattern" seen in reconstructed glomeruli [5][6][7][10] might now possibly be quantified by cycle structure.

With experimental evidence demonstrating the mechanisms of angiogenesis (vessel budding, anastomosis, and intussusception), these mechanisms can also be represented by graph theory. In particular, the random graph process of edge sprouting, splitting, and connecting, models the development of a glomerular network from a single vessel (edge).

Efforts to obtain accurate depictions of glomerular networks known at this time have resulted in graph-like illustrations, some of which are shown in Figures 9 to 11. We have computed the graph invariants: order (n), size (t), distance from afferent to efferent vertices (rd), cycle rank ($\beta = t - n + 1$), number of 3-cycles (c_3), and 3-cycle density (c_3/β). A summary of these graph invariants for six published reconstructed renal glomeruli are given in Table 6.

Investigators	n	t	rd	β	c_3	c_3/β
Shea (Figure 9)	195	320	12	126	10	.079
Wahl et al.	358	595	12	238	24	.100
Winkler et al. (Figure 10)	316	472	14	157	8	.051
Remuzzi et al.	247	403	12	157	18	.115
Nyengaard & Marcussen	264	434	12	171	7	.041
Antiga (Figure 11)	289	440	12	152	25	.164

Table 6. Values of n, t, rd, β, c_3, and c_3/β from known vascular networks.

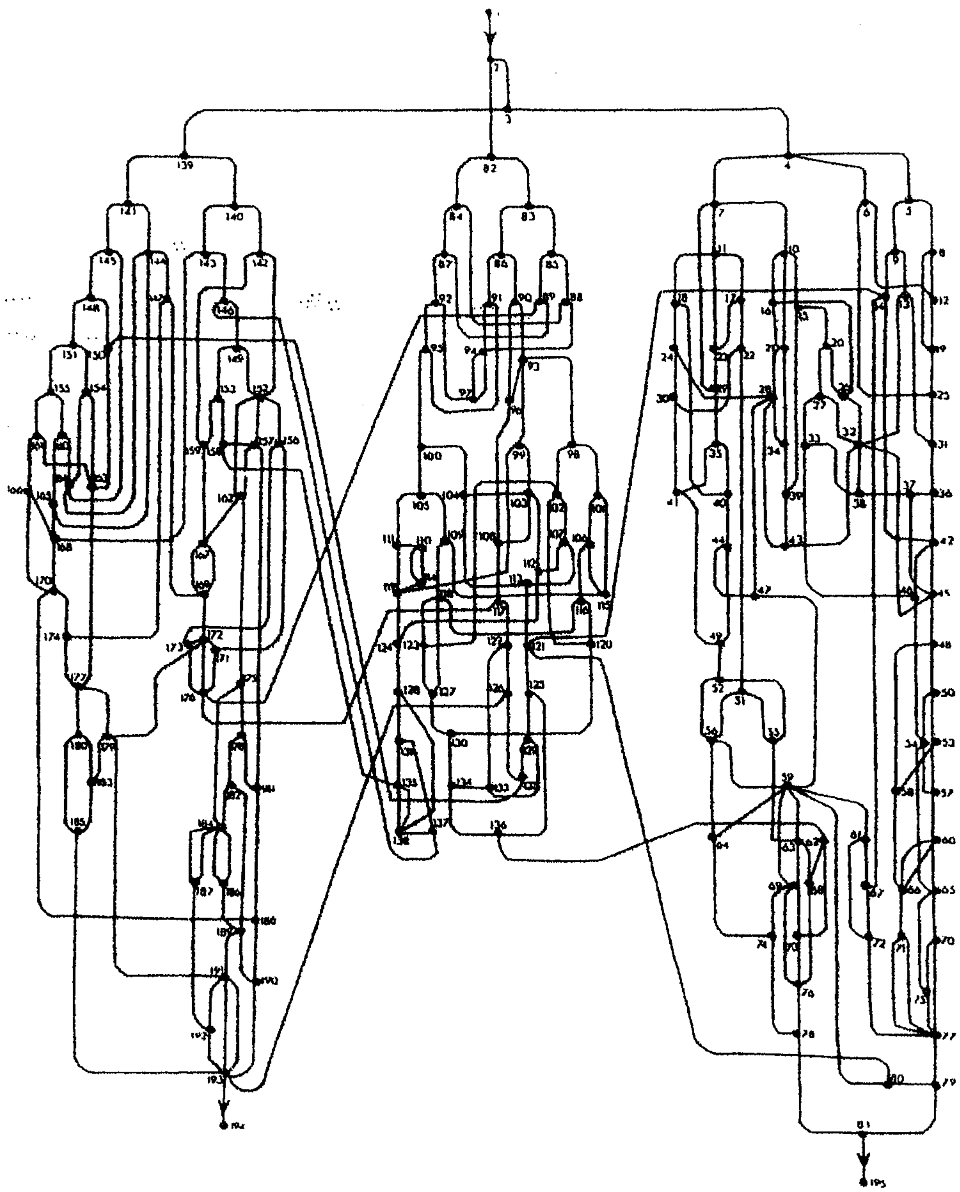

Figure 9. Graph depiction of a renal glomerular network by Shea[10].

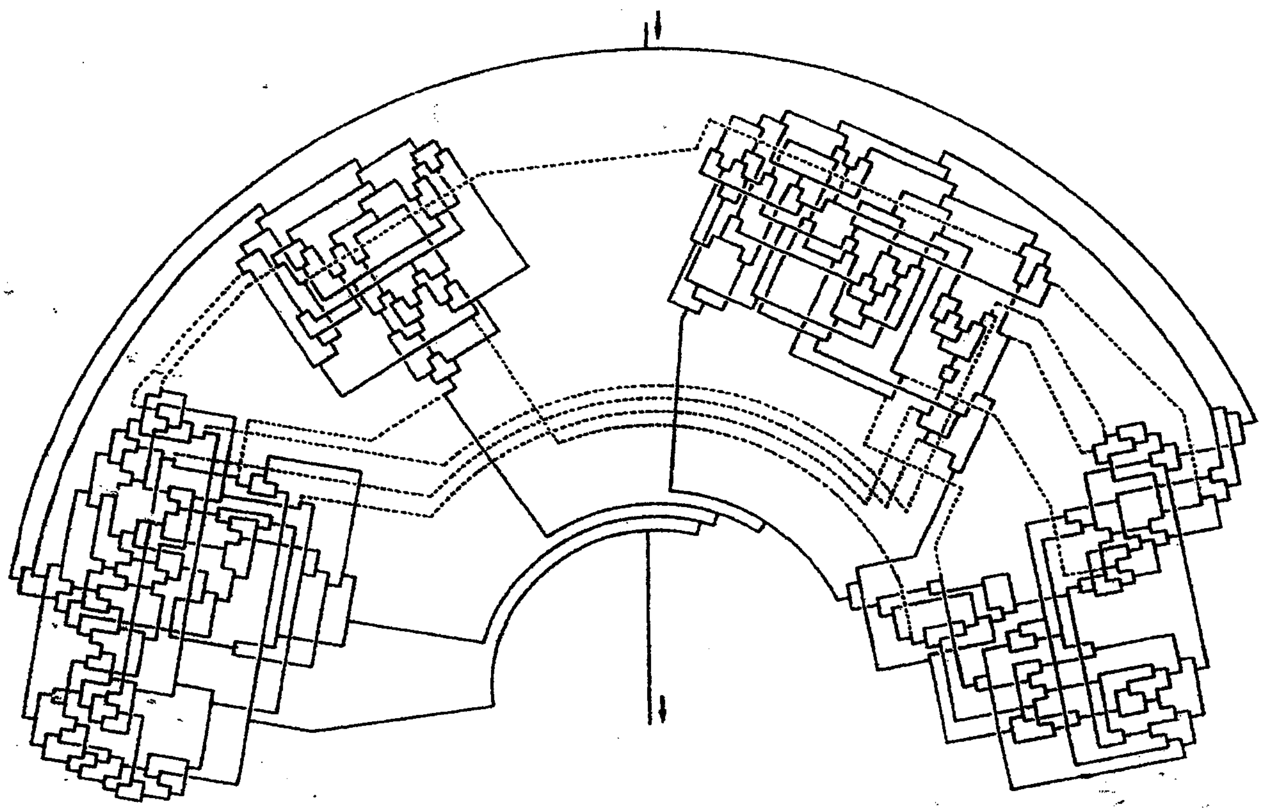

Figure 10. Graph-like depiction of a renal glomerular network by Winkler et al. [14].

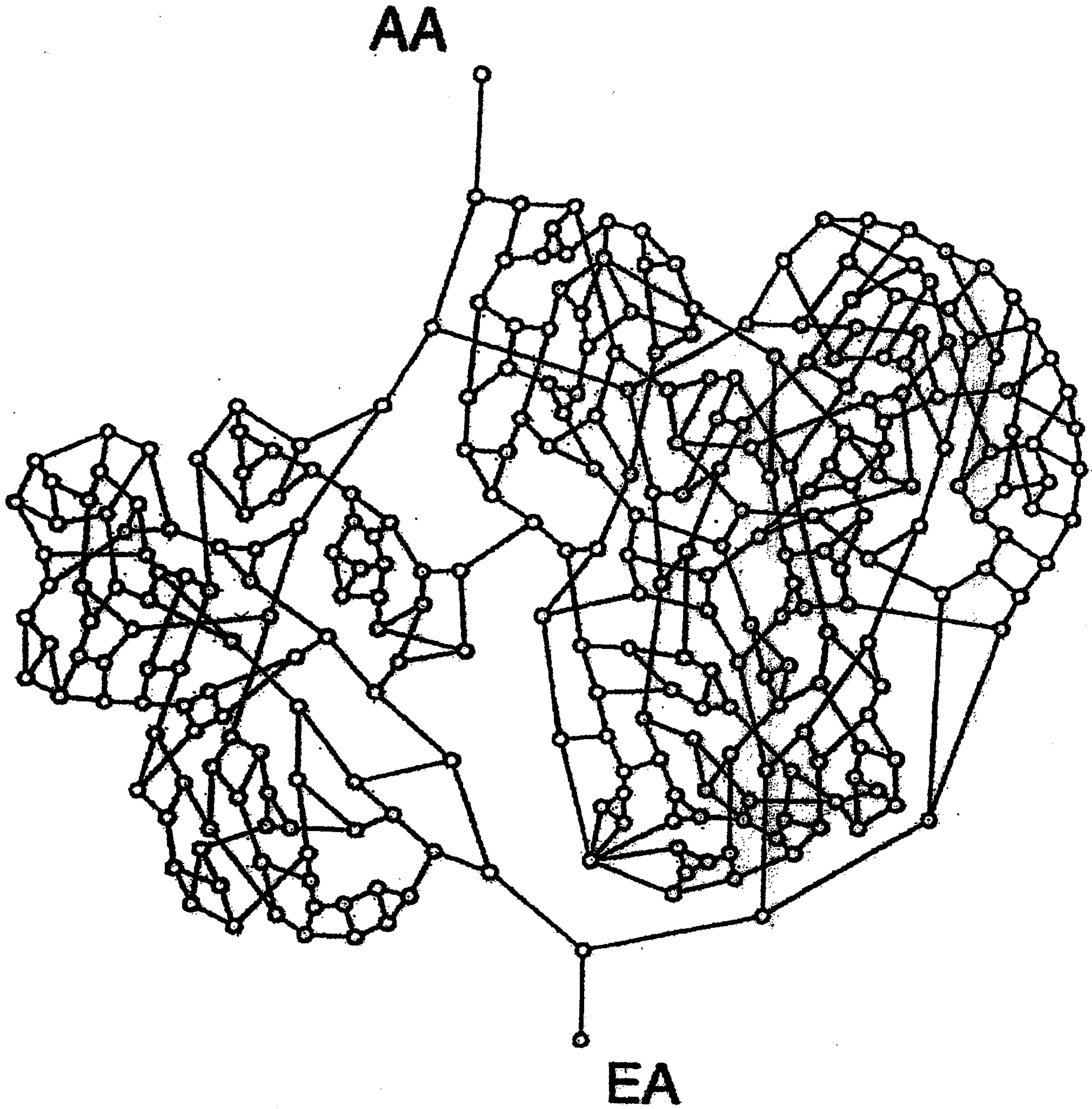

Figure 11. Graph depiction of a renal glomerular network by Antiga et al. [1].

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