ALGEBRAIC AND DISCRETE MATHEMATICAL METHODS FOR MODERN BIOLOGY

RAINA ROBEVA, EDITOR

Algebraic and Discrete Mathematical Methods for Modern Biology

Edited by

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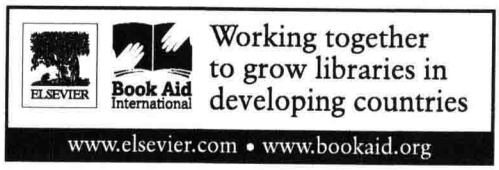

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Preface

In the last 15 years, the field of modern biology has been transformed by the use of new mathematical methods, complementing and driving biological discoveries. Problems from gene regulatory networks and genomics, RNA folding, infectious disease and drug resistance modeling, phylogenetics, and ecological networks and food webs have increasingly benefited from the application of discrete mathematics and computational algebra. Modern algebra approaches have proved to be a natural fit for many problems where the use of traditional dynamical models built with differential equations is not appropriate or optimal.

While the use of modern algebra methods is now in the mainstream of mathematical biology research, this trend has been slow to influence the undergraduate mathematics and biology curricula, where difference and differential equation models still dominate. Several high-profile reports have been released in the past 5 years, including Refs. [1–3], calling urgently for broadening the undergraduate exposure at the interface of mathematics and biology, and including methods from modern discrete mathematics and their biological applications. However, those reports have been slow to elicit the transformative change in the undergraduate curriculum that many of us had hoped for. The anemic response may be attributed to a relative lack of educational undergraduate resources that highlight the critical impact of algebraic and discrete mathematical methods on contemporary biology. It is this niche that our book seeks to fill.

The format of this volume follows that of our earlier book, *Mathematical Concepts and Methods in Modern Biology: Using Modern Discrete Methods*, Robeva and Hodge (Editors), published in 2013 by Academic Press. At the time of its planning, we considered the modular format of that text (with chapters largely independent from one another) experimental, but we felt reassured when the book was selected as 1 of 12 contenders for the 2013 Society of Biology Awards in its category. We have adopted the same format here, as we believe that it provides readers and instructors with the independence to choose biological topics and mathematical methods that are of greatest interest to them.

Due to the modular format, the order of the chapters in the volume does not necessarily imply an increased level of difficulty or the need for more prerequisites for the later chapters. When chapters are connected by a common biological thread, they are grouped together, but they can still be used independently. Each chapter begins with a question or a number of related questions from modern biology, followed by the description of certain mathematical methods and theory appropriate in the search of answers. As in our earlier book, chapters can be viewed as fast-track pathways through the problem, which start by presenting the biological foundation, proceed by covering the relevant mathematical theory and presenting numerous examples, and end by highlighting connections with ongoing research and current publications. The level of presentation varies among chapters—some may be appropriate for introductory courses, while others may require more mathematical or biological background. Exercises are embedded within the text of each chapter, and their execution requires only material discussed up to that point. In addition, many chapters feature challenging open-ended questions (designated as projects) that provide starting points for explorations appropriate for undergraduate research, and supply references to relevant publications from the recent literature. In their most general form, some of the projects feature truly open questions in mathematical biology.

The book's companion website (http://booksite.elsevier.com/9780128012130) contains solutions to the exercises, as well all figures and relevant data files for the examples and exercises in the chapters. In addition, the site hosts software code, project guidelines, online supplements, appendices, and tutorials for selected chapters. The specialized software utilized throughout the book highlights the critical importance of computing

applications for visualization, simulation, and analysis in modern biology. We have been careful to feature software that is in the mainstream of current mathematical biology research, while also being mindful of giving preference to freely available software.

We hope that the book will be a valuable resource to mathematics and biology programs, as it describes methods from discrete mathematics and modern algebra that can be presented, for the most part, at a level completely accessible to undergraduates. Yet the book provides extensions and connections with research that would also be helpful to graduate students and researchers in the field. Some of the material would be appropriate for mathematics courses such as finite mathematics, discrete structures, linear algebra, abstract/modern algebra, graph theory, probability, bioinformatics, statistics, biostatistics, and modeling, as well as for biology courses such as genetics, cell and molecular biology, biochemistry, ecology, and evolution.

The selection of topics for the volume and the choice of contributors grew out of the workshop "Teaching Discrete and Algebraic Mathematical Biology to Undergraduates" organized by Raina Robeva, Matthew Macauley, and Terrell Hodge and funded and hosted by the Mathematical Biosciences Institute (MBI) on July 29-August 2, 2013 at The Ohio State University. The editor and contributors of this volume greatly appreciate the encouragement and assistance received from the MBI's leadership and staff. Without their support, this volume would not have been possible. We also acknowledge with gratitude the support of the National Institute for Mathematical and Biological Synthesis (NIMBioS) in providing an opportunity to further test selected materials as part of the tutorial "Algebraic and Discrete Biological Models for Undergraduate Courses" offered on June 18-20, 2014 at NIMBioS.

I would like to express my personal thanks to all contributors who embraced the project early on and committed time and energy into producing the chapter modules for this unconventional textbook. Your enthusiasm for the project was remarkable, and you have my deep gratitude for the dedication and focus with which you carried it out. My special thanks also go to Daniel Hrozencik and Timothy Comar for providing feedback on a few of the chapter drafts. I am indebted to the editorial and production teams at Elsevier and particularly to the book's editors, Paula Callaghan and Katey Birtcher, our editorial project managers, Sarah Watson and Amy Clark, and our production manager, Vijayaraj Purushothaman. It has been a pleasure and a privilege to work with all of you. Finally, I would like to thank my husband, Boris Kovatchev, for his patience and support throughout.

Raina S. Robeva
October 20, 2014

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- All figures from the book
- Solutions to all exercises
- Computer code, data files, and links to software and materials carefully chosen to supplement the content of the textbook
- Appendices, tutorials, and additional projects for selected chapters

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Chapter 1

Graph Theory for Systems Biology: Interval Graphs, Motifs, and Pattern Recognition

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1.1 INTRODUCTION

Systems thinking is perceived as an important contemporary challenge of education [1]. However, *systems biology* is an old and inclusive term that connotes many different subareas of biology. Historically two important threads were synchronic: (a) the systems ecology of the Odum school [2–4], which was developed in the context of engineering principles applied to ecosystems [5, 6], and (b) systems physiology that used mechanical principles [7] to understand organs as mechanical devices integrated into the circulatory system, digestive system, anatomical system, immune system, nervous system, etc. For example, the heart could be thought of as a pump, the kidney as a filter, the lung as a bellows, the brain as a wiring circuit (or later as a computer), elbow joints as hinges, and so on. It should be noted that both areas extensively employed *ordinary* and *partial differential equations* (ODEs and PDEs). Indeed, some systems physiologists argued that all mathematical biology should be based on the application of PDEs. On the other hand, evolutionary biologists argued that these diachronic systems approaches too often answered only "how" questions that investigated optimal design principles and did not address "why" questions focusing on the constraints of historical contingency.

Not surprisingly, one of the leading journals in the field—*Frontiers in Systems Biology*—announces in its mission statement, [8] "Contrary to the reductionist paradigm commonly used in Molecular Biology, in Systems Biology the understanding of the behavior and evolution of complex biological systems need not necessarily be based on a detailed molecular description of the interactions between the system's constituent parts." Therefore, in this chapter we emphasize two major macroscopic and global aspects of contemporary systems biology: (i) the graph-theoretic relationships between components in networks and (ii) the relationship of these patterns to the historical contingencies of evolutionary constraints. Numerous articles and several books [9, 10] exist on graph theory and its application to systems biology, so the reader may ask what are we doing in this chapter that is different. Our main purpose is to help biologists, mathematicians, students, and researchers recognize which graph-theoretic tools are appropriate for different kinds of questions, including quantitative analyses of interactions for mining large data sets, visualizing complex relationships, modeling the consequences of perturbation of networks, and testing hypotheses.

Every network construct in systems biology is a hypothesis. For example, Rios and Vendruscolo [11] describe the network hypothesis as the assumption "according to which it is possible to describe a cell through the set of interconnections between its component molecules." They then conclude, "it becomes convenient to focus on

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these interactions rather than on the molecules themselves to describe the functioning of the cell." In this chapter, we go a step further. We believe that a mathematical biology perspective also studies such questions as: Which molecules are involved? What do they do functionally? What is their three-dimensional structure? Where are they located in a cell? We stress that every network and pathway that we discuss is a useful construct from a biological perspective. They do not exist *per se* inside of cells. Imagine a series of biological macromolecules (proteins, nucleic acids, polysaccharides) that are crowded and colliding with one another in a suspension. The networks and pathways for the interactions between these molecules constructed by biologists may represent preferred associations defined by tighter bindings of specific macromolecules or the product of a reaction catalyzed by one macromolecule (an enzyme) as the starting material (substrate) of another enzyme. Thus, biologists have already drawn mathematical diagrams and graphs in the sense that they have abstracted, generalized, and symbolized a set or relationships.

Too often biologists produce networks as visualizations without further analysis. In this chapter, using Excel and Java-based software that we have developed, we show readers how to make mathematical measurements (average degree, diameter, clustering coefficient, etc.) and discern holistic properties (small world versus scale-free, see Hayes [12] for a complete overview) of the networks being studied and visualized, and obtain insights that are relevant and meaningful in the context of systems biology. We show how the network hypothesis can be investigated by complementary and supplementary mathematical and biological perspectives to yield key insights and help direct and inform additional research.

Palsson [10] suggests that twenty-first century biology will focus less on the reductionist study of components and more on the integration of systems analysis. He identifies four principles in his "systems biology paradigm": "First, the list of biological components that participated in the process of interest is enumerated. Second, the interactions between these components are studied and the 'wiring diagrams' of genetic circuits are constructed .... Third, reconstructed network[s] are described mathematically and their properties analyzed.... Fourth, the models are used to analyze, interpret, and predict biological experimental outcomes." Here, we assume that the first two steps exist in databases or published articles; this allows us to focus on the mathematics of the third step as a way that allows biologists to better direct their work on the fourth step. Thus, the goals for this chapter are as follows.

- Learn how graph theory can be used to help obtain meaningful insights into complex biological data sets.
- Analyze complex biological networks of diverse types (restriction maps, food webs, gene expression, disease etiology) to detect patterns of relationships.
- Visualize ordering of modules/motifs within complex biological networks by first testing the applicability of simple linear approaches (interval graphs).
- Demonstrate that even when strict mathematical assumptions do not apply fully to a given biological data set, there is still benefit in applying an analytical approach because of the power of the human mind to discern prominent patterns in data rearranged through the application of mathematical transformations.
- Show that the visualizations help biologists obtain insights into their data, examine the significance of outliers, mine databases for additional information about observed associations, and plan further experiments.

To accomplish this, we first emphasize *how* graph theory is a natural fit for biological investigations of relationships, patterns, and complexity. Second, graph theory lends itself easily to questions about *what* biologists should be looking for among representations of relationships. We introduce concepts of hubs, maximal cliques, motifs, clusters, interval graphs, complementary graphs, ordering, transitivity, Hamiltonian circuits, and consecutive ones in adjacency matrices. Finally, graph theory helps us interrogate *why* these relationships are occurring. Basically, we examine the triptych of form, function, and phylogeny to differentiate between evolutionary and engineering constraints.

The chapter is structured as follows. We begin by introducing some background concepts from graph theory that will be utilized later in the chapter. We then introduce interval graphs through two biological examples related to chromosome sequencing and food webs. The rest of the chapter is devoted to two extended examples of biological questions related to recently published studies on gene expression and disease etiology. The analyses

for those examples demonstrate how graph theory can help illuminate concepts of biological importance. Each of the examples is followed by suggestions for open-ended projects in pursuit of similar analyses of related biological questions and data.

1.2 REVISUALIZING, RECOGNIZING, AND REASONING ABOUT RELATIONSHIPS

Graph theory has enormous applicability to biology. It is particularly powerful in this era of terabytes of data because it allows a tremendous topological reduction in complexity and investigation of patterns. The applications of graph theory in mathematical biology, several of which are illustrated in this chapter, include subcellular localization of coordinated metabolic processes, identification of hubs central to such processes and the links between them, analysis of flux in a system, temporal organization of gene expression, the identification of drug targets, determination of the role of proteins or genes of unknown function, and coordination of sequences of signals. Medical applications include diagnosis, prognosis, and treatment. We will see below that by reducing a biological exploration to a relevant graph representation, we are able to examine, study, and measure various quantitative and meta-properties of the resulting graph and to obtain insights into why particular biological processes such as gene-gene, protein-protein, signal-detector-effector, and predator-prey occur.

1.2.1 Basic Concepts from Graph Theory

A *graph* in mathematics is a collection of *vertices* connected by *edges*. Graphs are often used in biology to represent networks and, more generally, to represent relationships between objects. The objects of interest are the vertices of the network, usually depicted as geometrical shapes such as dots, circles, or squares, while the connections between them are represented by the edges. In an applied context, the vertices are generally labeled. Vertices u and v that are directly connected by an edge are called *adjacent vertices* or *neighbors*. A subgraph that consists of all vertices adjacent to a vertex u and all edges connecting any two such vertices forms the *neighborhood of the vertex u*. For each graph, one can construct its *complementary graph:* a graph that has the same vertices as the original graph, but such that vertices u and v are adjacent in the complementary graph if and only if u and v are not adjacent in the original graph.

If a vertex u is related to itself, the edge connecting u with itself is called a *loop*. A *path* is a sequence of edges connecting neighboring vertices and the *length of a path* is the number of edges it uses. Loops could be considered paths of length 1 that start and end in the same vertex. We say that a vertex u in a graph is *connected* to vertex v if there is a path from u to v. An undirected graph is a *connected graph* if a pathway exists from every vertex to every other vertex. Otherwise, the graph is *disconnected*. A *Hamiltonian path* is a path that goes through all vertices in the graph and visits each vertex exactly once. A graph in which any two vertices are connected by a unique path is called a *tree*.

If there is directional dependence (e.g., "u activates v"; "u is the parent of v" as opposed to "u and v are friends"), then the direction is represented by an arrow. Graphs with directional dependencies are called *directed graphs*. Paths in directed graphs must follow the direction of the edges. The number of edges connected to a vertex u represents the *degree of the vertex* (loops are usually counted twice). In a directed graph, a vertex is called a *source* when all of its edges are outgoing edges; it is called a *sink* when all of its edges are incoming edges. The *in-degree* of a vertex is the number of incoming edges to the vertex and the *out-degree* is defined by the number of outgoing edges. Thus, the degree of each vertex in a directed graph is the sum of the in-degree and out-degree. Vertices with degrees among the top 5% in a network are often characterized as *hubs*. As hubs have a large number of neighbors, they often perform important roles in many biological networks.

Additional graph-theoretical definitions and properties that we will use in a substantive way in the chapter are:

- *Clique*—a subgraph is a graph in which every vertex is connected by an edge to any other vertex in the subgraph; a *maximal clique* is a clique that cannot be extended by including an additional adjacent vertex; in other words a maximal clique is a clique that is not a subset of a larger clique.

- *Diameter of a graph*—the maximum number of edges that have to be traversed to go from one vertex to another in a graph using shortest paths, i.e., the *longest* shortest path in the graph.
- *Degree distribution of a graph*—the probability distribution of the vertex degrees over the whole graph. It is represented as a histogram, in which the probability p_k that a vertex has degree k is represented by the proportion of the nodes in the graph with degree k. When $p_k = Ck^{-a}$, where a is a constant and C is a normalizing factor, the degree distribution follows a *power law*.
- *Connectivity of a graph*—the minimum number of edges that need to be removed from a connected graph to obtain a graph that is no longer connected. The connectivity of a graph is an important measure of its robustness as a network.
- *Clustering coefficient of a network*—we will not provide a mathematically rigorous definition here but, heuristically speaking, it represents the degree to which nodes in a graph tend to cluster together. In its local version, the clustering coefficient of a vertex quantifies how close its neighbors are to being a clique. The mathematical definition and further details can be found in Chapter 5 [13]
- *Transitively oriented graphs*—directed graphs in which if three vertices are connected in a triangle, and two successive edges are in the same direction, then a third edge must be present and go from the first to the third vertex.
- *Small world network*—A large graph with a relatively small number of neighbors in which any two vertices are connected by a path of relatively short length.

It has been hypothesized [12] that many real world networks, including biological networks, are *small world networks* that are in between lattice (highly ordered) and completely random networks, with properties that promote efficient information transfer and retrieval. In particular, such networks exhibit three unique properties: (a) they are usually sparse, i.e., they have relatively few edges compared to vertices; (b) they have large average clustering coefficients; and (c) a relatively small diameter on the order of $\log N$, where N is the number of vertices in the network [12]. The usual popularization of small world networks draws attention to two features: (a) every vertex is connected to every other vertex through relatively few edges ("six degrees of separation," "the Kevin Bacon problem," "what is your Erdös number?") and (b) it only takes a few "weak" links (i.e., edges that connect distant clusters) to create this effect. Much attention in mathematical biology has been paid to the question of why small world networks are manifested and have evolved at so many different levels of biological systems.

- *Interval graphs*—a special class of graphs that can be depicted as a family of intervals positioned along the real line.

Interval graphs are an interesting case because a biologist first developed them, and the formal mathematics to explore them was developed later. Interval graphs have a variety of biological applications across broad samplings of phylogenetic diversity, spatial and temporal scales, and diverse biological mechanisms.

In order to understand how interval graphs are constructed, we begin from the experimental biological determination of which intervals of finite lengths (fragments, sequences, deletions, etc.) overlap one another. Consider a hypothetical dataset with eight overlapping fragments (I_1 through I_8) as the intervals. All pairwise overlap relations are determined and an "adjacency" matrix is constructed (Figure 1.1a). The entry in the ith row and jth column is 1, if the vertices i and j are adjacent (fragments overlap) and 0 otherwise. The *adjacency matrix* is a square symmetric matrix. Next, we generate an undirected graph called the *intersection graph* (Figure 1.1b) in which the rows and the columns are labeled by the graph's vertices in the following way: each interval corresponds to a vertex and two vertices u and v are connected with an edge if and only if the intervals u and v overlap. Note that this property of interval graphs also has another interesting matrix formulation. As we will see later, it is equivalent to the *consecutive ones* property of matrices.

Finally, we determine the maximal cliques from the intersection graphs—in this case we determine that there are five such cliques (A, B, C, D, and E) by visual inspection—and set up a different binary matrix M where the rows represent the maximal cliques in the graph and the entry at the kth row and the rth column of M is 1, if vertex r belongs to the kth maximal clique, and is 0 otherwise. The line representation of the resulting interval graph is shown in Figure 1.1c.

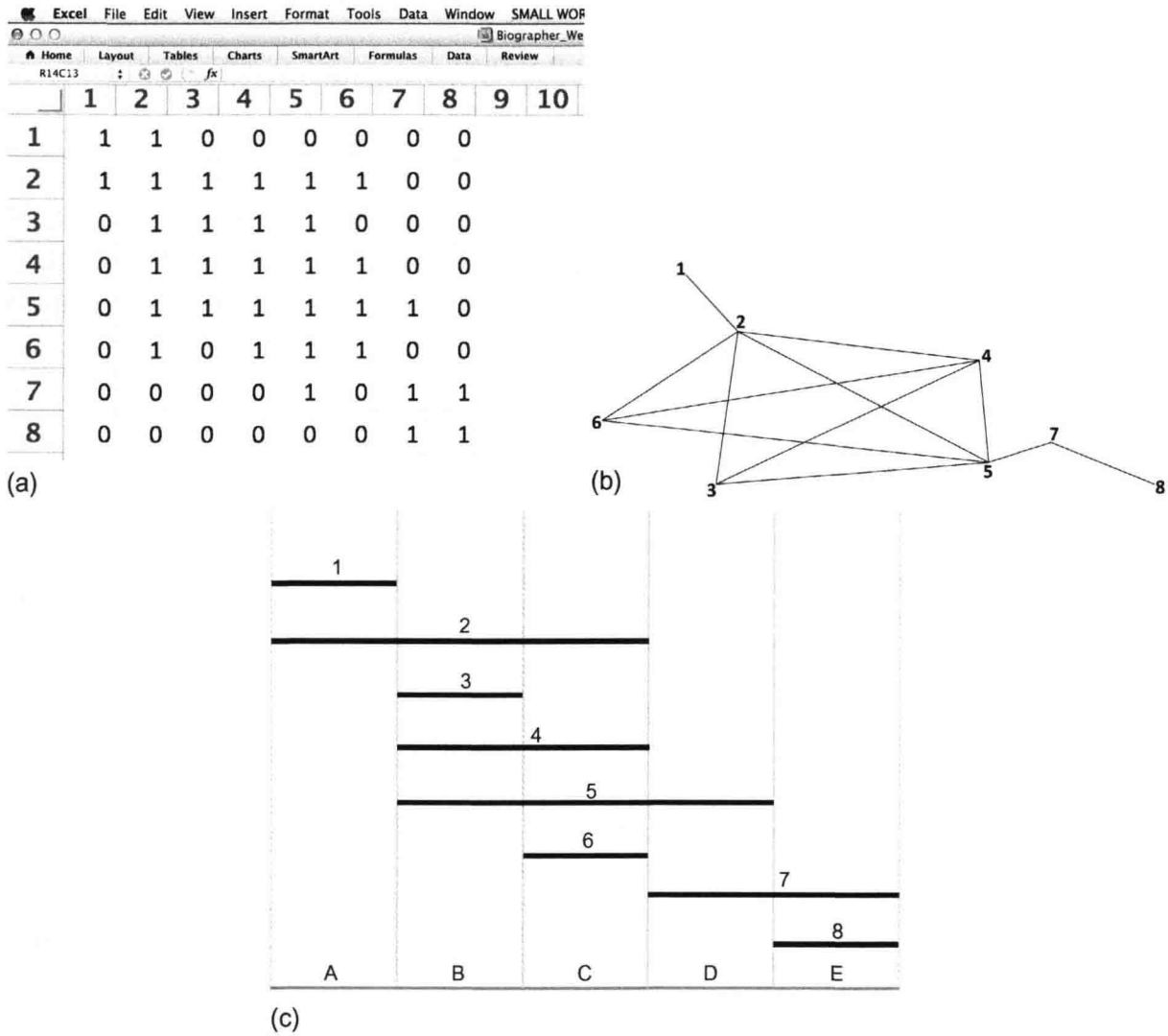

FIGURE 1.1 The connection between adjacency matrices, intersection graphs, and interval graphs. (a) The adjacency matrix from the experimental biological determination of which intervals of finite lengths (fragments, sequences, deletions, etc.) overlap one another. (b) The corresponding intersection graph of the adjacency matrix connects two vertices u and v with an edge if and only if the intervals u and v overlap. (c) An interval graph is a set of intervals of finite lengths arranged along a line where the rows represent the intervals of finite lengths (fragments, sequences, deletions, etc.) and the columns are labeled at the bottom according to the maximal cliques in the intersections graph (Maximal Clique A: 1 and 2; Maximal Clique B: 2, 3, 4, and 5; Maximal Clique C: 2, 4, 5, and 6; Maximal Clique D: 5 and 7; Maximal Clique E: 7 and 8). Note that there should be no horizontal gap between adjacent maximal cliques as that would mean that we have information that cliques which are not maximal exist in such regions (e.g., in Panel c, if interval 5 were shortened on its right end and interval 8 were shortened on its left end, there would be a clique between intervals 5 and 8 that only contained interval 7 which is obviously not maximal because it is contained in both D and E, each of which contains more members).

An important property of interval graphs is that their maximal cliques can be ordered in sequence in such a way that for any vertex (interval) v, the maximal cliques containing v occur consecutively in the sequence. Consider Figure 1.1c, where the maximal cliques for the interval graph are represented by regions between vertical line segments. The five maximal cliques A, B, C, D, E are ordered in a way where, for example, the three cliques containing interval I_5 (B,C, D) appear in a sequence; the three cliques containing I_2 (A, B, C) appear in a sequence; the two cliques containing I_7 (E,D) appear in a sequence, and so on. The matrix M is called the *clique matrix* for the intersection graph, and is shown below with row labels corresponding to the cliques and column labels corresponding to vertices (intervals) added for clarity: