V11 Metabolic networks - Graph connectivity

Graph connectivity is related to analyzing biological networks for
- finding cliques
- edge betweenness
- modular decomposition

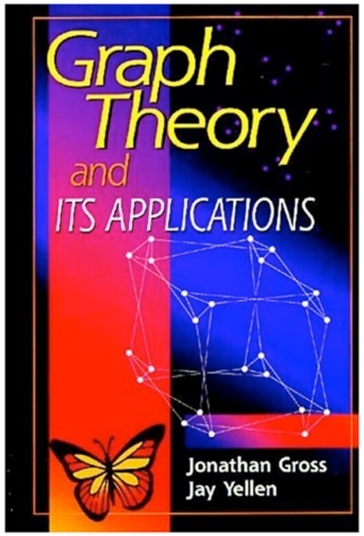
that have been or will be covered in forthcoming lectures.

Cut-sets are related to breaking up metabolic networks.

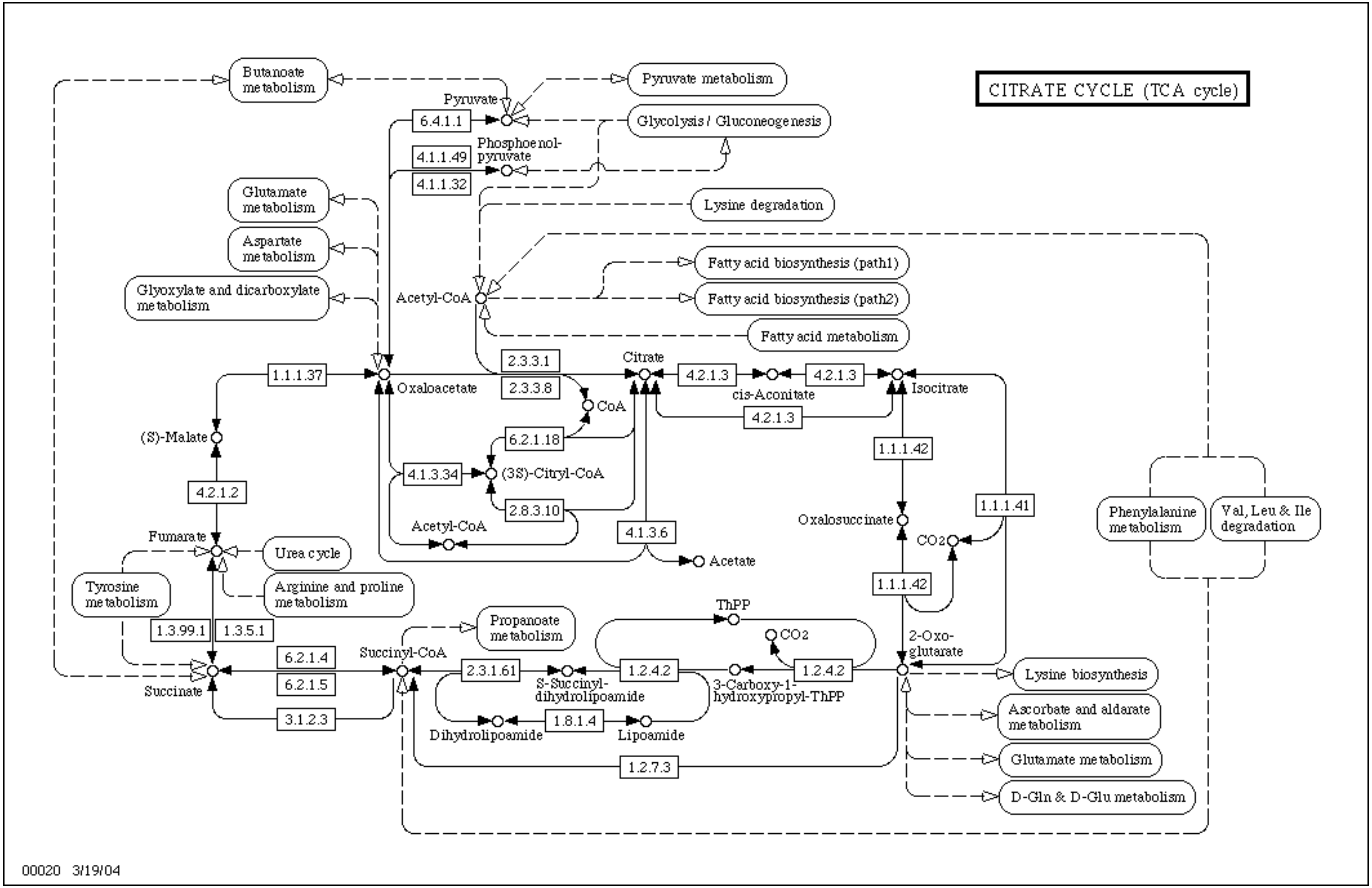
<u>Today's program</u>

V11 closely follows chapter 5.1 in the book
on the right on „Vertex- and Edge-Connectivity"

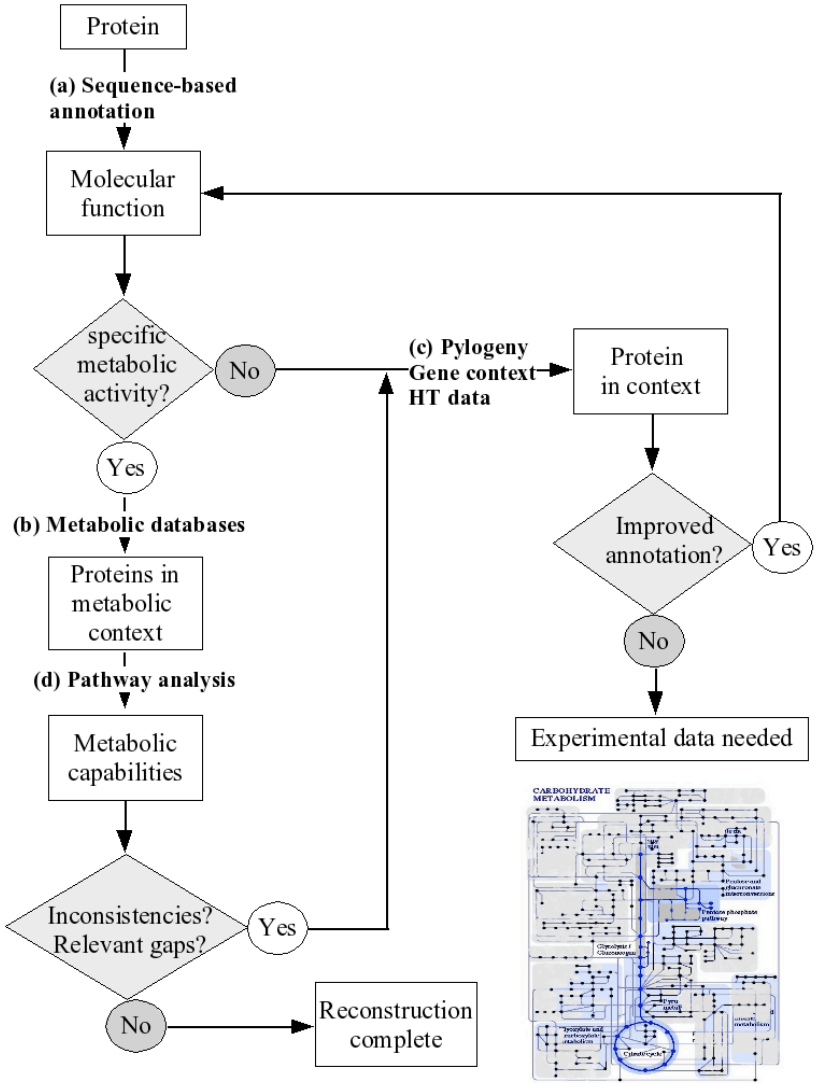
V12 will cover parts of chapter 5.3 on
„Max-Min Duality and Menger's Theorems"



Citrate Cycle (TCA cycle) in E.coli



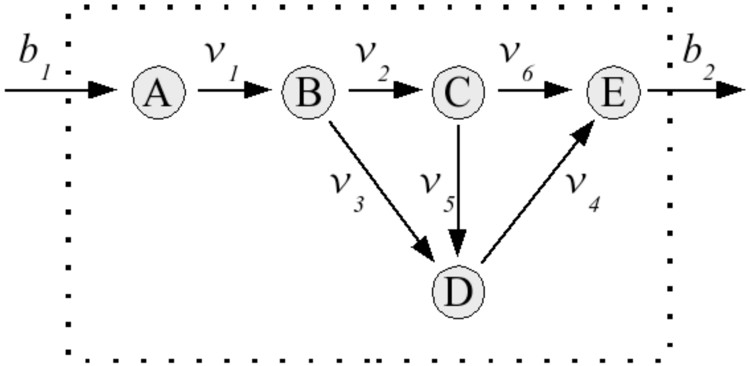
What people do ?

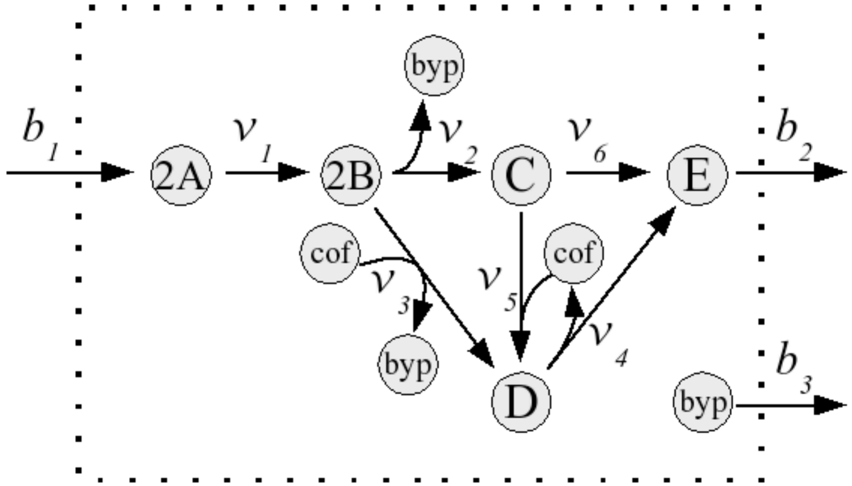


Analysis of metabolic networks is at a relatively advanced/complete stage compared to protein-interaction networks or gene-regulatory networks.

Possible reason:
Most cellular metabolites are known.

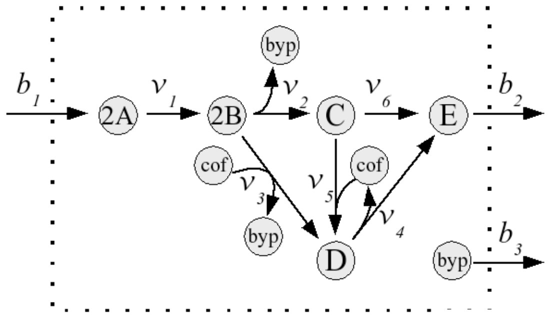
Motivation – simple networks – task 1



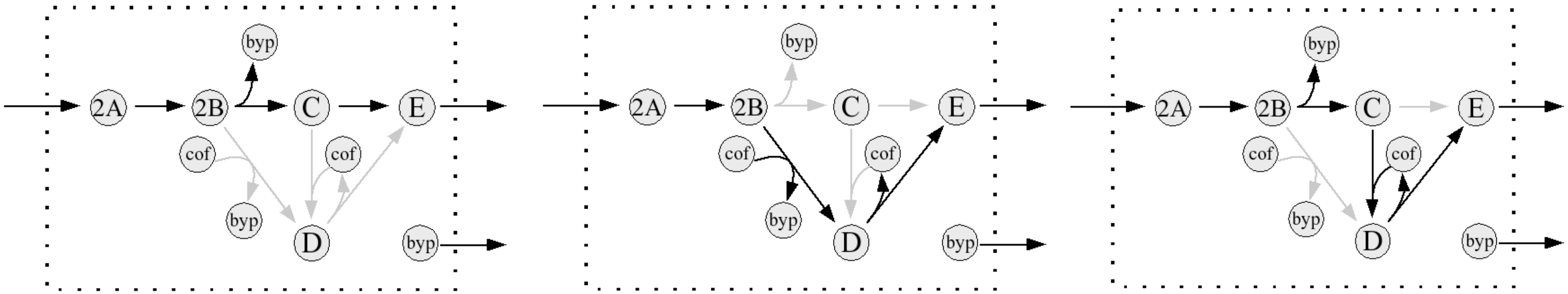


What are all the possible **steady-state flux distributions** (v_1, v_2, v_3, v_4, v_5, v_6) in these networks?

Flux distributions: linear combinations of extreme pathways



Compute **extreme pathways** („eigen vector basis" of metabolic network):

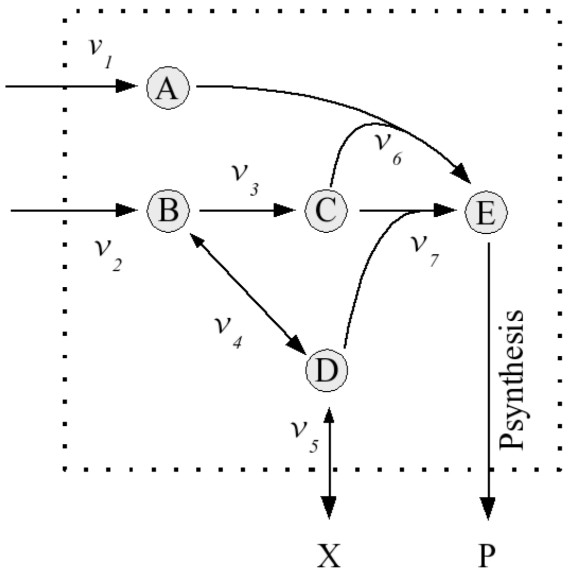


Each of these extreme pathways leaves concentrations of internal metabolites unchanged.

These are all extreme pathways of this network.

➔ All flux distributions in this network that can be written as linear combinations of these 3 extreme pathways are feasible steady-state flux distributions, but not others.

Motivation – simple networks – task 2

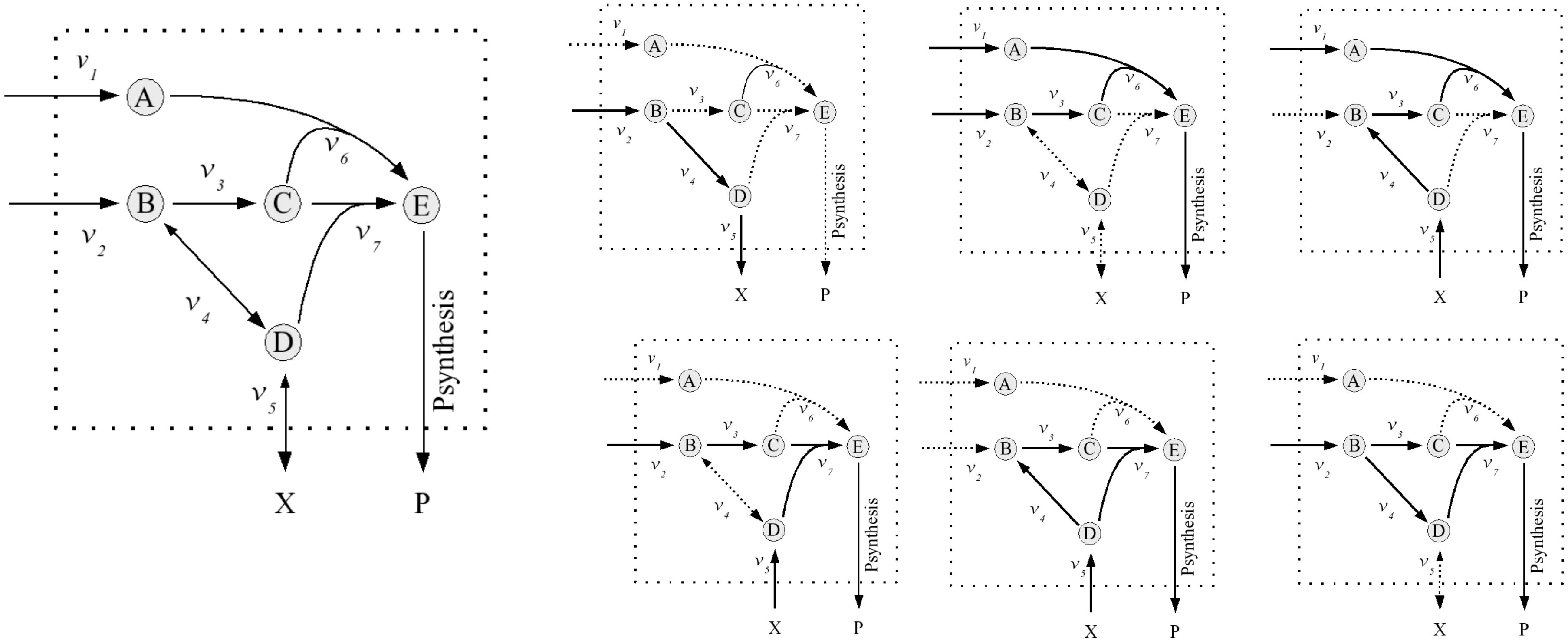


v_1 – v_7 are the reaction fluxes of 7 reactions in this network
that are catalyzed by transporters or enzymes 1 – 7.

P is the product of interest of this network.

What is the minimal number of reactions that need to be deleted (by gene knockouts or small molecule inhibitors) to block synthesis of P?

Characterize all minimal cut sets



The system contains 6 elementary flux modes.

5 of them are coupled to synthesis of P.

Each of these must be disconnected by deleting the smallest possible number of reactions ➔ find all minimal cut sets, take the smallest one.

Motivation: graph connectedness

Some connected graphs are „more connected“ than others.

E.g. some connected graphs can be disconnected
by the removal of a single vertex or a single edge,
whereas others remain connected
unless more vertices or more edges are removed.

→ use **vertex-connectivity** and **edge-connectivity**
to **measure** the **connectedness** of a graph.

Motivation: graph connectedness

Determining the number of edges (or vertices) that must be removed to disconnect a given connected graph applies directly to analyzing the **vulnerability** of existing networks.

Definition: A graph is **connected** if for every pair of vertices *u* and *v*, there is a walk from *u* to *v*.

Definition: A **component** of *G* is a maximal connected subgraph of *G*.

Vertex- and Edge-Connectivity

Definition: A **vertex-cut** in a graph *G* is a vertex-set *U* such that *G* – *U* has more components than *G*.

A **cut-vertex** (or cutpoint) is a vertex-cut consisting of a single vertex.

Definition: An **edge-cut** in a graph *G* is a set of edges *D* such that *G* – *D* has more components than *G*.

A **cut-edge** (or bridge) is an edge-cut consisting of a single edge.

The **vertex-connectivity** of a connected graph *G*, denoted $\kappa_v(G)$, is the minimum number of vertices whose removal can either disconnect *G* or reduce it to a 1-vertex graph.

→ if *G* has at least one pair of non-adjacent vertices, then $\kappa_v(G)$ is the size of a smallest vertex-cut.

Vertex- and Edge-Connectivity

Definition: A graph *G* is **k-connected** if *G* is connected and $\kappa_v(G) \geq k$.
If *G* has non-adjacent vertices, then *G* is *k*-connected
if every vertex-cut has at least *k* vertices.

Definition: The edge-connectivity of a connected graph *G*, denoted $\kappa_e(G)$,
is the minimum number of edges whose removal can disconnect *G*.

→ if G is a connected graph,
the edge-connectivity $\kappa_e(G)$ is the size of a smallest edge-cut.

Definition: A graph *G* is *k*-edge-connected if *G* is connected and
every edge-cut has at least *k* edges (i.e. $\kappa_e(G) \geq k$).

Vertex- and Edge-Connectivity

Example: In the graph below, the vertex set $\{x,y\}$ is one of three different 2-element vertex-cuts. There is no cut-vertex. $\rightarrow \kappa_v(G) = 2$.

The edge set $\{a,b,c\}$ is the unique 3-element edge-cut of graph G, and there is no edge-cut with fewer than 3 edges. Therefore $\kappa_e(G) = 3$.

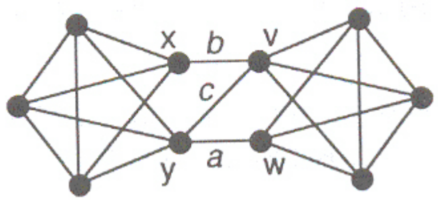


Figure 5.1.1 A graph G with $\kappa_v(G) = 2$ and $\kappa_e(G) = 3$.

Application: The connectivity measures κ_v and κ_e are used in a quantified model of **network survivability**, which is the capacity of a network to retain connections among its nodes after some edges or nodes are removed.

Vertex- and Edge-Connectivity

Since neither the vertex-connectivity nor the edge-connectivity of a graph is affected by the existence or absence of self-loops, we will assume in the following that all graphs are loopless.

Proposition 5.1.1 Let *G* be a graph. Then the edge-connectivity $\kappa_e(G)$ is less than or equal to the minimum degree δ_{min} (G).

Proof: Let *v* be a vertex of graph *G* with degree $k = \delta_{min}(G)$.
Then, the deletion of the *k* edges that are incident on vertex separates *v* from the other vertices of *G*. □

Vertex- and Edge-Connectivity

<u>Definition</u>: A collection of distinct non-empty subsets $\{S_1, S_2, ..., S_l\}$ of a set A is a **partition** of A if both of the following conditions are satisfied:

(1) $S_i \cap S_j = \emptyset$, $\forall\ 1 \le i < j \le l$
(2) $\cup_{i=1...l}\ S_i = A$

<u>Definition</u>: Let G be a graph, and let X_1 and X_2 form a partition of V_G.

The set of all edges of G having one endpoint in X_1 and the other endpoint in X_2 is called a **partition-cut** of G and is denoted $\langle X_1, X_2 \rangle$.

Partition Cuts and Minimal Edge-Cuts

<u>Proposition</u> 4.6.3: Let $\langle X_1, X_2 \rangle$ be a partition-cut of a connected graph G.

If the subgraphs of G induced by the vertex sets X_1 and X_2 are connected, then $\langle X_1, X_2 \rangle$ is a minimal edge-cut.

<u>Proof</u>: The partition-cut $\langle X_1, X_2 \rangle$ is an edge-cut of G, since X_1 and X_2 lie in different components of $G - \langle X_1, X_2 \rangle$.

Is it minimal?

Let S be a proper subset of $\langle X_1, X_2 \rangle$, and let edge $e \in \langle X_1, X_2 \rangle - S$.
By definition of $\langle X_1, X_2 \rangle$, one endpoint of e is in X_1 and the other endpoint is in X_2.

Thus, if the subgraphs induced by the vertex sets X_1 and X_2 are connected, then $G - S$ is connected.

Therefore, S is not an edge-cut of G, which implies that $\langle X_1, X_2 \rangle$ is a minimal edge-cut. □

Partition Cuts and Minimal Edge-Cuts

Proposition 4.6.4. Let S be a minimal edge-cut of a connected graph G, and let X_1 and X_2 be the vertex-sets of the two components of $G - S$.
Then $S = \langle X_1, X_2 \rangle$.

Proof: Clearly, $S \subset \langle X_1, X_2 \rangle$, i.e. every edge $e \in S$ has one endpoint in X_1 and one in X_2. Otherwise, the two endpoints would either both belong to X_1 or to X_2. Then, S would not be minimal because $S - e$ would also be an edge-cut of G.

On the other hand, if $e \in \langle X_1, X_2 \rangle$ - S, then its endpoints would lie in the same component of $G - S$, contradicting the definition of X_1 and X_2. □

Remark: This assumes that the removal of a minimal edge-cut from a connected graph creates exactly two components.

Partition Cuts and Minimal Edge-Cuts

Proposition 4.6.5. A partition-cut $\langle X_1, X_2 \rangle$ in a connected graph G is a minimal edge-cut of G or a union of edge-disjoint minimal edge-cuts.

Proof: Since $\langle X_1, X_2 \rangle$ is an edge-cut of G, it must contain a minimal edge-cut, say S.

If $\langle X_1, X_2 \rangle \neq S$, then let $e \in \langle X_1, X_2 \rangle - S$, where the endpoints v_1 and v_2 of e lie in X_1 and X_2, respectively.

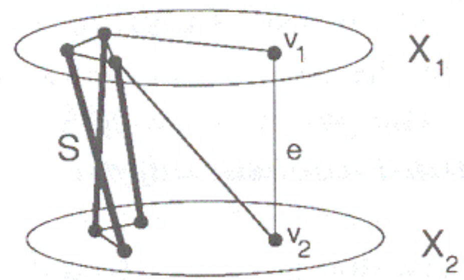


Figure 4.6.1

Since S is a minimal edge-cut, the X_1-endpoints of S are in one of the components of $G - S$, and the X_2-endpoints are in the other component.

Furthermore, v_1 and v_2 are in the same component of $G - S$ (since $e \in G - S$).

Suppose, wlog, that v_1 and v_2 are in the same component as the X_1-endpoints of S.

Partition Cuts and Minimal Edge-Cuts

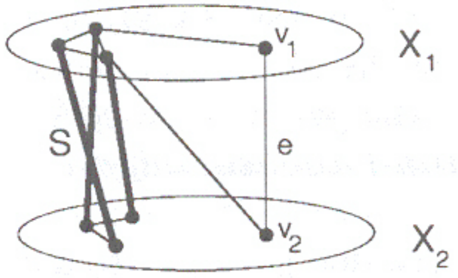


Figure 4.6.1

Then every path in G from v_1 to v_2 must use at least one edge of $\langle X_1,X_2\rangle$ - S.

Thus, $\langle X_1,X_2\rangle$ - S is an edge-cut of G and contains a minimal edge-cut R.

Appyling the same argument, $\langle X_1,X_2\rangle$ - $(S \cup R)$ either is empty or is an edge-cut of G.

Eventually, the process ends with $\langle X_1,X_2\rangle$ - $(S_1 \cup S_2 \cup \ldots S_r) = \varnothing$,
where the S_i are edge-disjoint minimal edge-cuts of G. □

Partition Cuts and Minimal Edge-Cuts

Proposition 5.1.2. A graph *G* is *k*-edge-connected
if and only if every partition-cut contains at least *k* edges.

Proof: (⇒) Suppose, that graph G is *k*-edge connected.
Then every partition-cut of G has at least *k* edges,
since a partition-cut is an edge-cut.

(⇐) Suppose that every partition-cut contains at least *k* edges.
By proposition 4.6.4., every minimal edge-cut is a partition-cut.
Thus, every edge-cut contains at least *k* edges. □

Relationship between vertex- and edge-connectivity

Proposition 5.1.3. Let e be any edge of a k-connected graph G, for $k \geq 3$.
Then the edge-deletion subgraph $G - e$ is $(k - 1)$-connected.

Proof: Let $W = \{w_1, w_2, ..., w_{k-2}\}$ be any set of $k - 2$ vertices in $G - e$,
and let x and y be any two different vertices in $(G - e) - W$.
It suffices to show the existence of an x-y walk in $(G - e) - W$.

First, suppose that at least one of the endpoints of edge e is contained in set W.
Since the vertex-deletion subgraph $G - W$ is 2-connected,
there is an x-y path in $G - W$.
This path cannot contain edge e.
Hence, it is an x-y path in the subgraph $(G - e) - W$.
Next suppose that neither endpoint of edge e is in set W.

Then there are two cases to consider.

Relationship between vertex- and edge-connectivity

Case 1: Vertices x and y are the endpoints of edge e.
Graph G has at least $k + 1$ vertices (since G is k-connected).
So there exists some vertex $z \in G - \{w_1, w_2, \ldots, w_{k-2}, x, y\}$.

Since graph G is k-connected, there exists
an x-z path P_1 in the vertex deletion subgraph $G - \{w_1, w_2, \ldots, w_{k-2}, y\}$ and
a z-y path P_2 in the subgraph $G - \{w_1, w_2, \ldots, w_{k-2}, x\}$

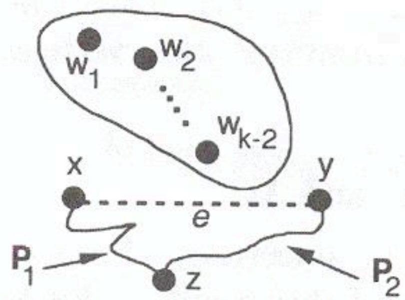


Figure 5.1.2 The existence of an x-y walk in $(G - e) - \{w_1, w_2, \ldots, w_{k-2}\}$.

Neither of these paths contains edge e, and, therefore,
their concatenation is an x-y walk in the subgraph $(G - e) - \{w_1, w_2, \ldots, w_{k-2}\}$

Relationship between vertex- and edge-connectivity

Case 2: At least one of the vertices x and y, say x, is not an endpoint of edge e.
Let u be an endpoint of edge e that is different from vertex x.
Since graph G is k-connected, the subgraph $G - \{w_1, w_2, ..., w_{k-2}, u\}$ is connected.

Hence, there is an x-y path P in $G - \{w_1, w_2, ..., w_{k-2}, u\}$.

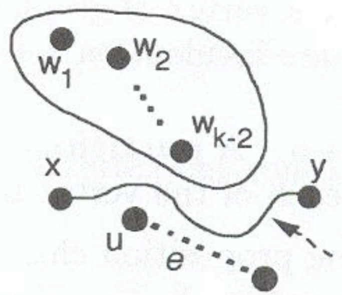


Figure 5.1.2 The existence of an x-y walk in $(G - e) - \{w_1, w_2, \ldots, w_{k-2}\}$.

It follows that P is an x-y path in $G - \{w_1, w_2, ..., w_{k-2}\}$ that does not contain vertex u and, hence excludes edge e
(even if P contains the other endpoint of e, which it could).

Therfore, P is an x-y path in $(G - e) - \{w_1, w_2, ..., w_{k-2}\}$. □

Relationship between vertex- and edge-connectivity

Corollary 5.1.4. Let G be a k-connnected graph, and let D be any set of m edges of G, for $m \leq k$ - 1. Then the edge-deletion subgraph $G - D$ is $(k - m)$-connected.

Proof: this follows from the iterative application of proposition 5.1.3. □

Corollary 5.1.5. Let G be a connected graph. Then $\kappa_e(G) \geq \kappa_v(G)$.

Proof. Let $k = \kappa_v(G)$, and let S be any set of $k - 1$ edges in graph G.
Since G is k-connected, the graph $G - S$ is 1-connected, by corollary 5.1.4.
Thus, the edge subset S is not an edge-cut of graph G,
which implies that $\kappa_e(G) \geq k$. □

Corollary 5.1.6. Let G be a connected graph. Then $\kappa_v(G) \leq \kappa_e(G) \leq \delta_{min}(G)$.

This is a combination of Proposition 5.1.1 and Corollary 5.1.5. □

Internally Disjoint Paths and Vertex-Connectivity: Whitney's Theorem

A communications network is said to be *fault-tolerant* if it has at least two alternative paths between each pair of vertices.
This notion characterizes 2-connected graphs.
A more general result for *k*-connected graphs follows later.

Terminology: A vertex of a path P is an **internal vertex** of P if it is neither the initial nor the final vertex of that path.

Definition: Let u and v be two vertices in a graph G.
A collection of u-v paths in G is said to be **internally disjoint** if no two paths in the collection have an internal vertex in common.

Internally Disjoint Paths and Vertex-Connectivity: Whitney's Theorem

Theorem 5.1.7 [Whitney, 1932] Let G be a connected graph with $n \geq 3$ vertices. Then G is 2-connected if and only if for each pair of vertices in G, there are two internally disjoint paths between them.

Proof: ($\Leftarrow$) Suppose that graph G is not 2-connected. Then let v be a cut-vertex of G. Since $G - v$ is not connected, there must be two vertices such that there is no x-y path in $G - v$. It follows that v is an internal vertex of every x-y path in G.

($\Rightarrow$) Suppose that graph G is 2-connected, and let x and y be any two vertices in G. We use induction on the distance $d(x,y)$ to prove that there are at least two vertex-disjoint x-y paths in G.

If there is an edge e joining vertices x and y, (i.e., $d(x,y) = 1$), then the edge-deletion subgraph $G - e$ is connected, by Corollary 5.1.4.

Thus, there is an x-y path P in $G - e$.

It follows that path P and edge e are two internally disjoint x-y paths in G.

Internally Disjoint Paths and Vertex-Connectivity: Whitney's Theorem

Next, assume for some $k \geq 2$ that the assertion holds for every pair of vertices whose distance apart is less than k. Let x and y be vertices such that distance $d(x,y) = k$, and consider an x-y path of length k.

Let w be the vertex that immediately precedes vertex y on this path, and let e be the edge between vertices w and y.

Since $d(x,w) < k$, the induction hypothesis implies that there are two internally disjoint x-w paths in G, say P and Q.

Also, since G is 2-connected, there exists an x-y path R in G that avoids vertex w.

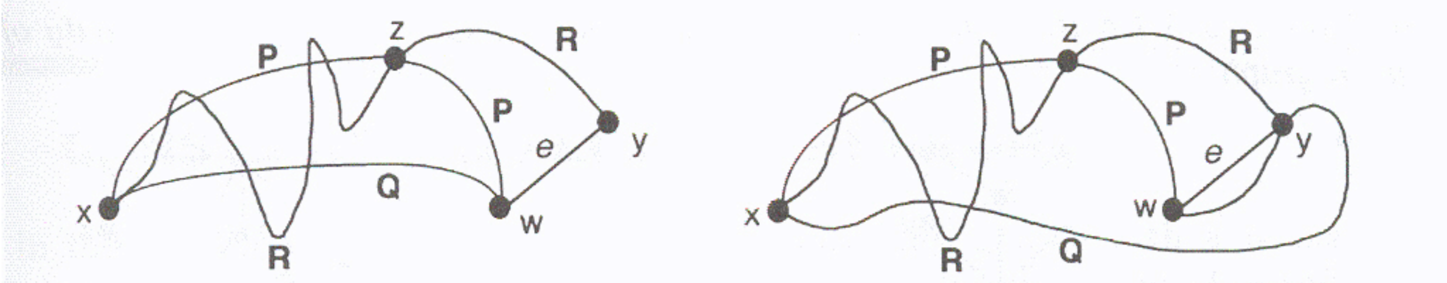


Figure 5.1.3

Path Q either contains vertex y (right) or it does not (left)

Internally Disjoint Paths and Vertex-Connectivity: Whitney's Theorem

Let *z* be the last vertex on path *R* that precedes vertex *y* and is also on one of the paths *P* or *Q* (*z* might be vertex *x*). Assume wlog that *z* is on path *P*.

Then *G* has two internally disjoint *x*-*y* paths. One of these paths is the concatenation of the subgraph of *P* from *x* to *z* with the subpath of *R* from *z* to *y*.

If vertex *y* is not on path *Q*, then a second *x*-*y* path, internally disjoint from the first one, is the concatenation of path *Q* with the edge *e* joining vertex *w* to vertex *y*.

If *y* is on path *Q*, then the subpath of *Q* from *x* to *y* can be used as the second path.

□

Internally Disjoint Paths and Vertex-Connectivity: Whitney's Theorem

Corollary 5.1.8. Let G be a graph with at least three vertices.
Then G is 2-connected if and only if any two vertices of G lie on a common cycle.

Proof: this follows from 5.1.7., since two vertices x and y lie on a common cycle if and only if there are two internally disjoint x-y paths.□