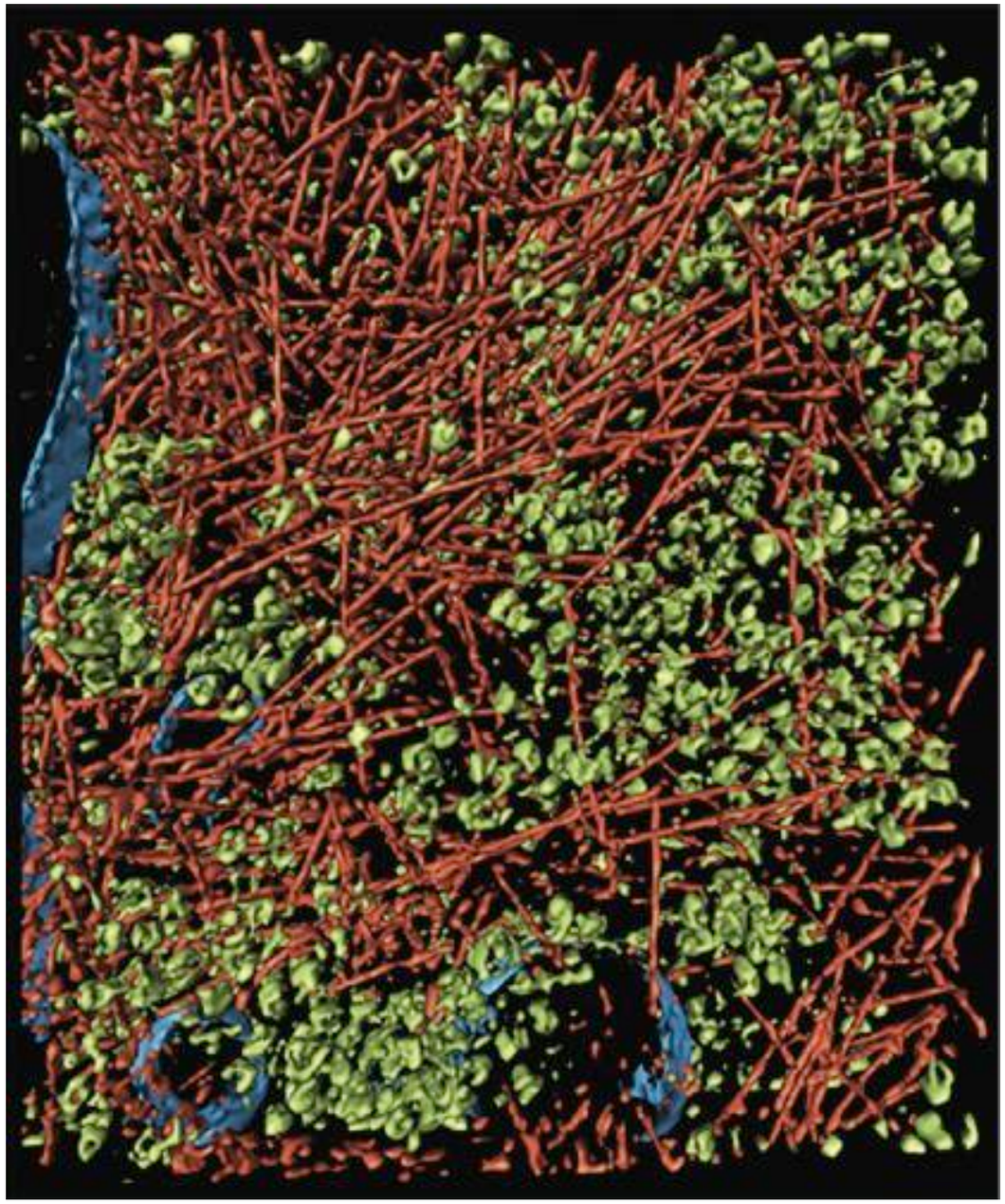
V1 - Introduction



Medalia et al, Science 298 (2002) 1209

A cell is a crowded environment
=> many different proteins,
metabolites, compartments, …

On a microscopic level
=> direct two-body interactions

At the macroscopic level
=> complex behavior

Can we understand the behavior from the interactions?

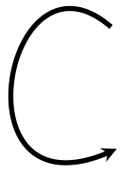
=> Connectivity

The view of traditional molecular biology

Molecular Biology: "One protein — one function"

mutation => phenotype

Linear one-way dependencies: regulation at the DNA level, proteins follow



DNA => RNA => protein => phenotype

Structural Biology: "Protein structure determines its function"

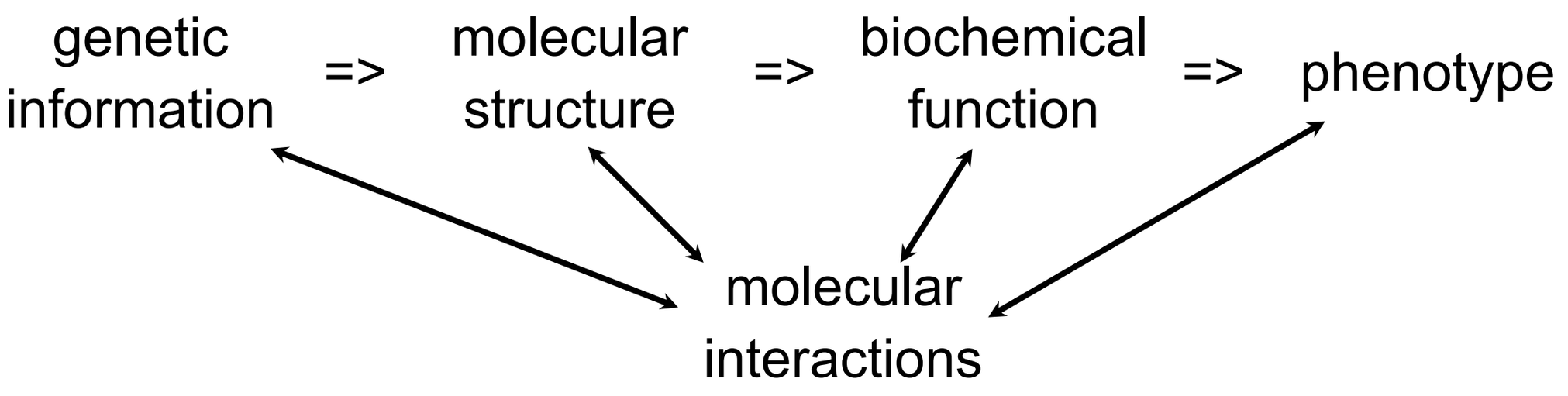
biochemical conditions => phenotype

No feedback, just re-action:

genetic information => molecular structure => biochemical function => phenotype

The Network View of Biology

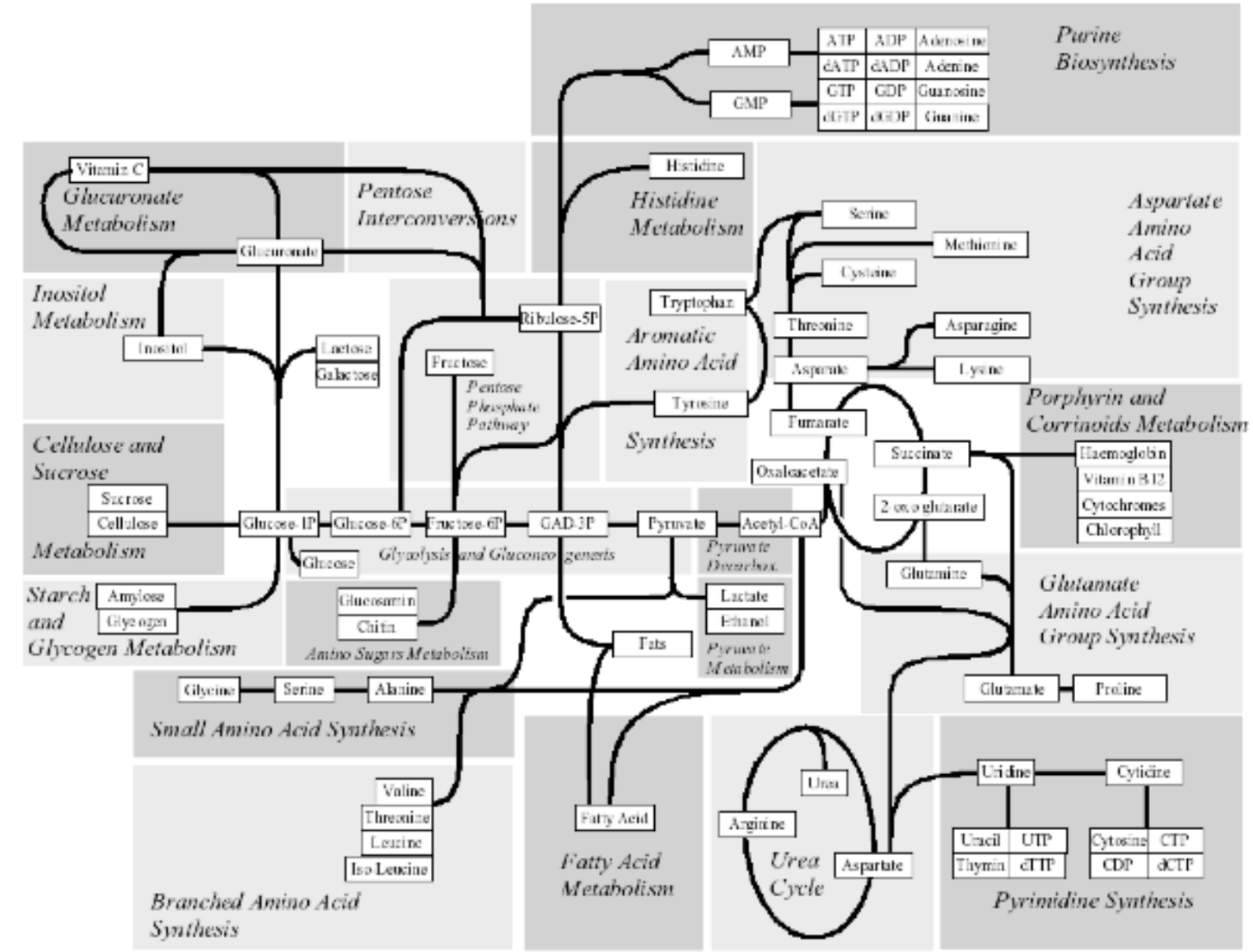
Molecular Systems Biology: "It's both + molecular interactions"



- highly connected network of various interactions, dependencies

=> study networks

Major Metabolic Pathways



static connectivity <=> dynamic response to external conditions <=> different states during the cell cycle

Schienennetzplan München

http://www.mvv-muenchen.de/de/netz-bahnhoefe/netzplaene/index.html

Lecture – Overview

Protein complexes: **spatial** structure

=> experiments, spatial fitting, docking

Protein association:

=> interface properties, spatial simulations

Protein-Protein-Interaction Networks: **pairwise** connectivity

=> data from experiments, quality check

PPI: static network **structure**

=> network measures, clusters, modules, …

Gene regulation: cause and **response**

=> Boolean networks

Metabolic networks: steady state of **large networks**

=> FBA, extreme pathways

Metabolic networks / signaling networks: **dynamics**

=> ODEs, modules, stochastic effects

Systems Biology

Appetizer: A whole-cell model for the life cycle of the human pathogen *Mycoplasma genitalium*

Theory

Cell

A Whole-Cell Computational Model Predicts Phenotype from Genotype

Jonathan R. Karr,[1,4] Jayodita C. Sanghvi,[2,4] Derek N. Macklin,[2] Miriam V. Gutschow,[2] Jared M. Jacobs,[2] Benjamin Bolival, Jr.,[2] Nacyra Assad-Garcia,[3] John I. Glass,[3] and Markus W. Covert[2,*]
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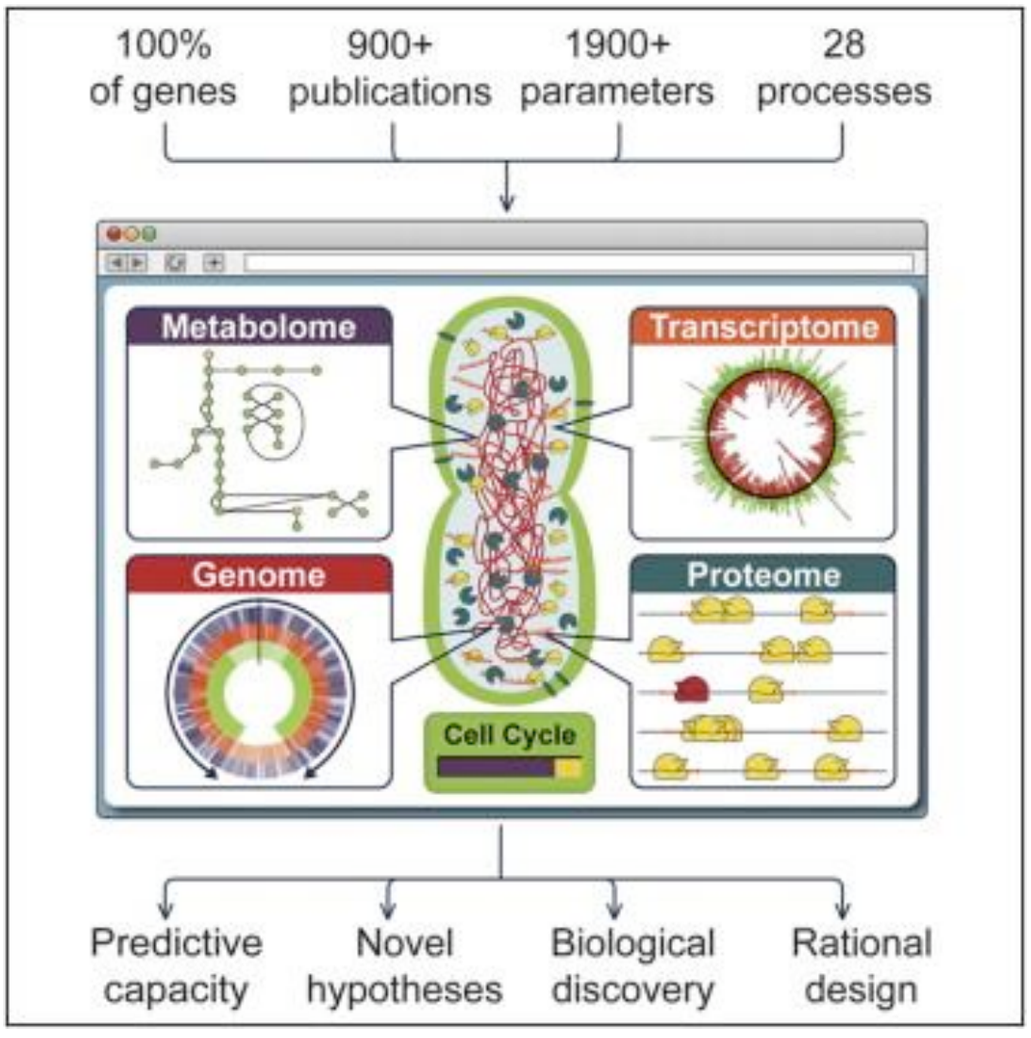
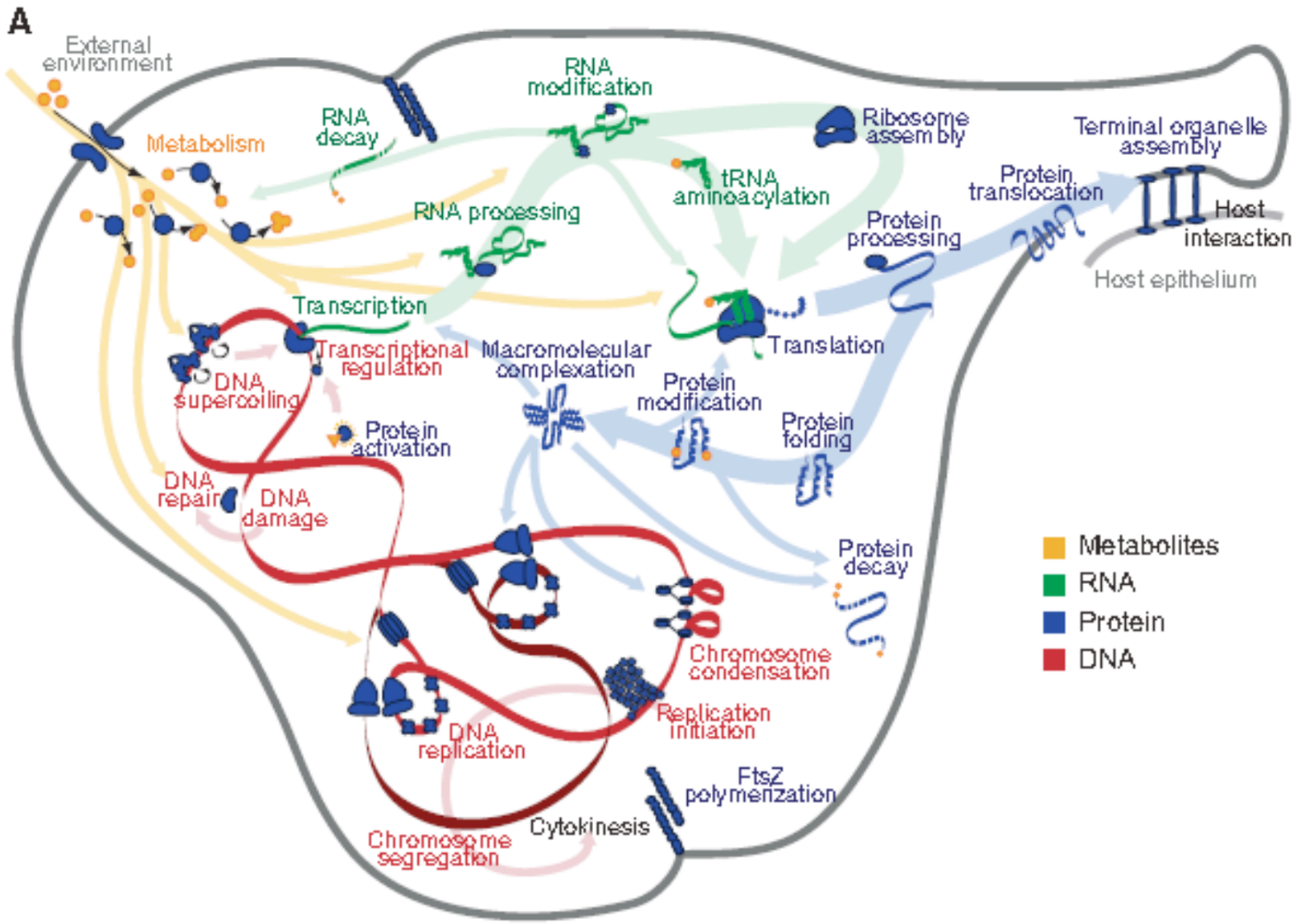
http://dx.doi.org/10.1016/j.cell.2012.05.044



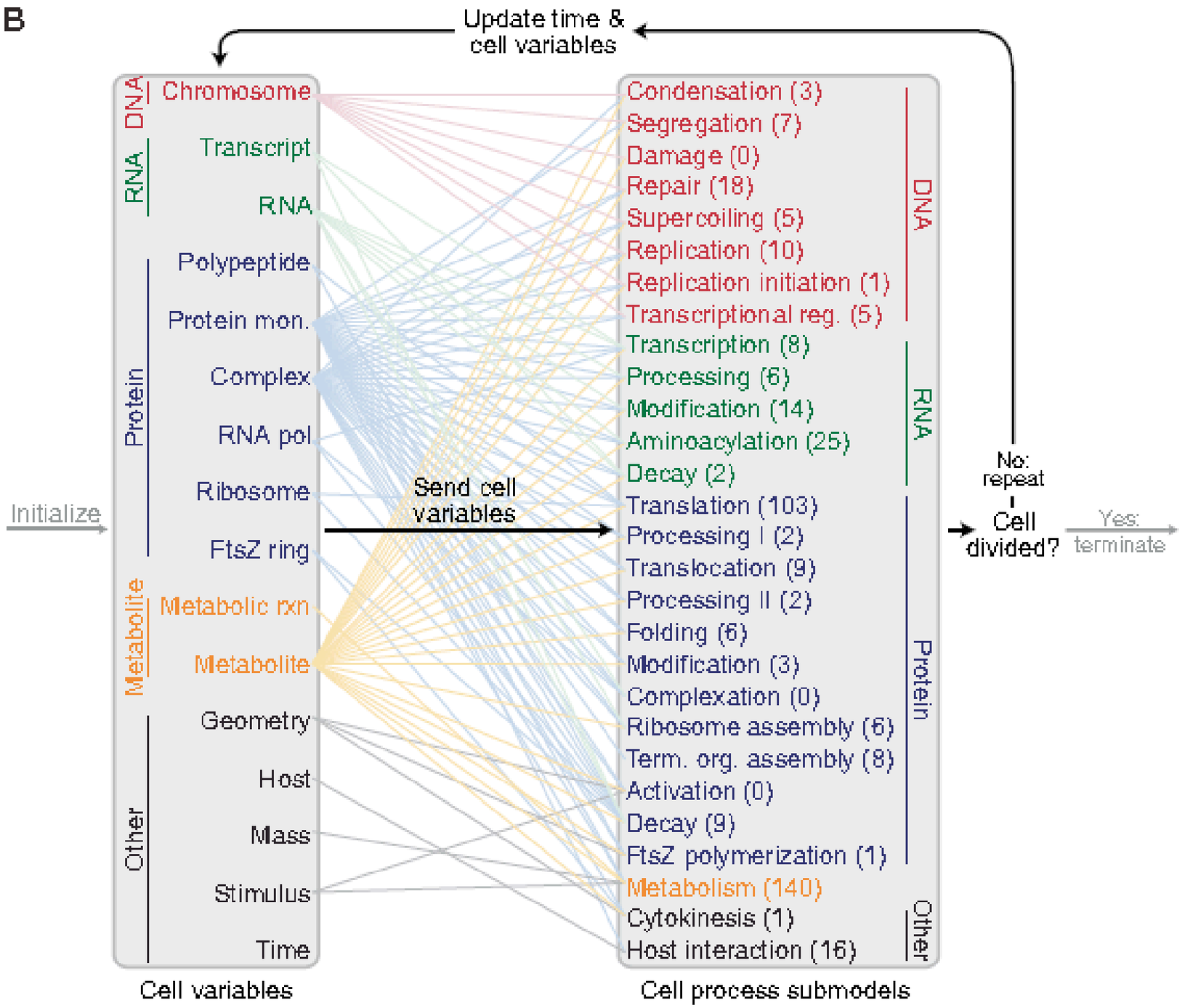
Cell 150, 389-401 (2012)

Divide and conquer approach (Caesar): split whole-cell model into 28 independent submodels



28 submodels are built / parametrized / iterated independently

Cell variables



System state is described by 16 cell variables

Colored lines: cell variables affected by individual submodels

Mathematical tools:

-Differential equations

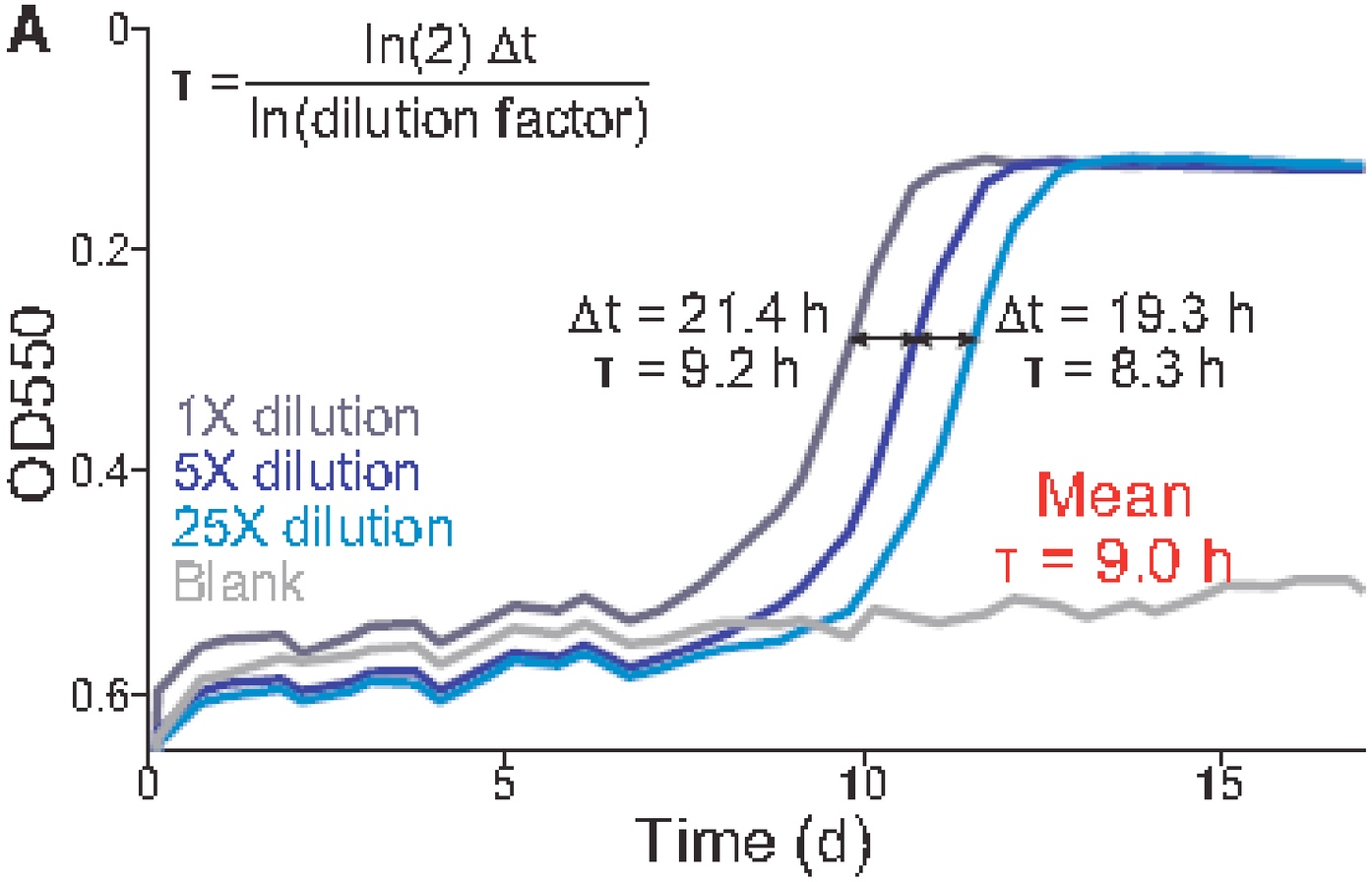
-Stochastic simulations

-Flux balance analysis

List S1. Primary sources of the *M. genitalium* reconstruction.

Data source	Content
Bernstein *et al.*, 2002[602]	mRNA half-lives
BioCyc[6]	Genome annotation, metabolic reactions
BRENDA[570]	Reaction kinetics
CMR[168]	Genome annotation
Deuerling *et al.*, 2003[388]	Chaperone substrates
DrugBank[847]	Antibiotics
Eisen *et al.*, 1999[891]	DNA repair
Endo *et al.*, 2007[391]	Chaperone substrates
Feist *et al.*, 2007[558]	Metabolic reactions
Glass *et al.*, 2006[193]	Gene essentiality
Güell *et al.*, 2009[418]	Transcription unit structure
Gupta *et al.*, 2007[280]	N-terminal methionine cleavage
KEGG[113]	Genome annotation, orthology
Kerner *et al.*, 2005[389]	Chaperone substrates
Krause *et al.*, 2004[409]	Terminal organelle assembly
Lindahl *et al.*, 2000[462]	DNA damage
Morowitz *et al.*, 1962[870]	Cell chemical composition
NCBI Gene[61,777]	Genome annotation
Neidhardt *et al.*, 1990[393]	Cell chemical composition
Peil, 2009[105]	RNA modification
PubChem[587]	Metabolite structures
SABIO-RK[100]	Reaction kinetics
Solabia[754–759]	Media chemical composition
Suthers *et al.*, 2009[610]	Metabolic reactions
UniProt[96]	Genome annotation
Weiner *et al.*, 2000[411]	Promoters
Weiner *et al.*, 2003[569]	mRNA expression

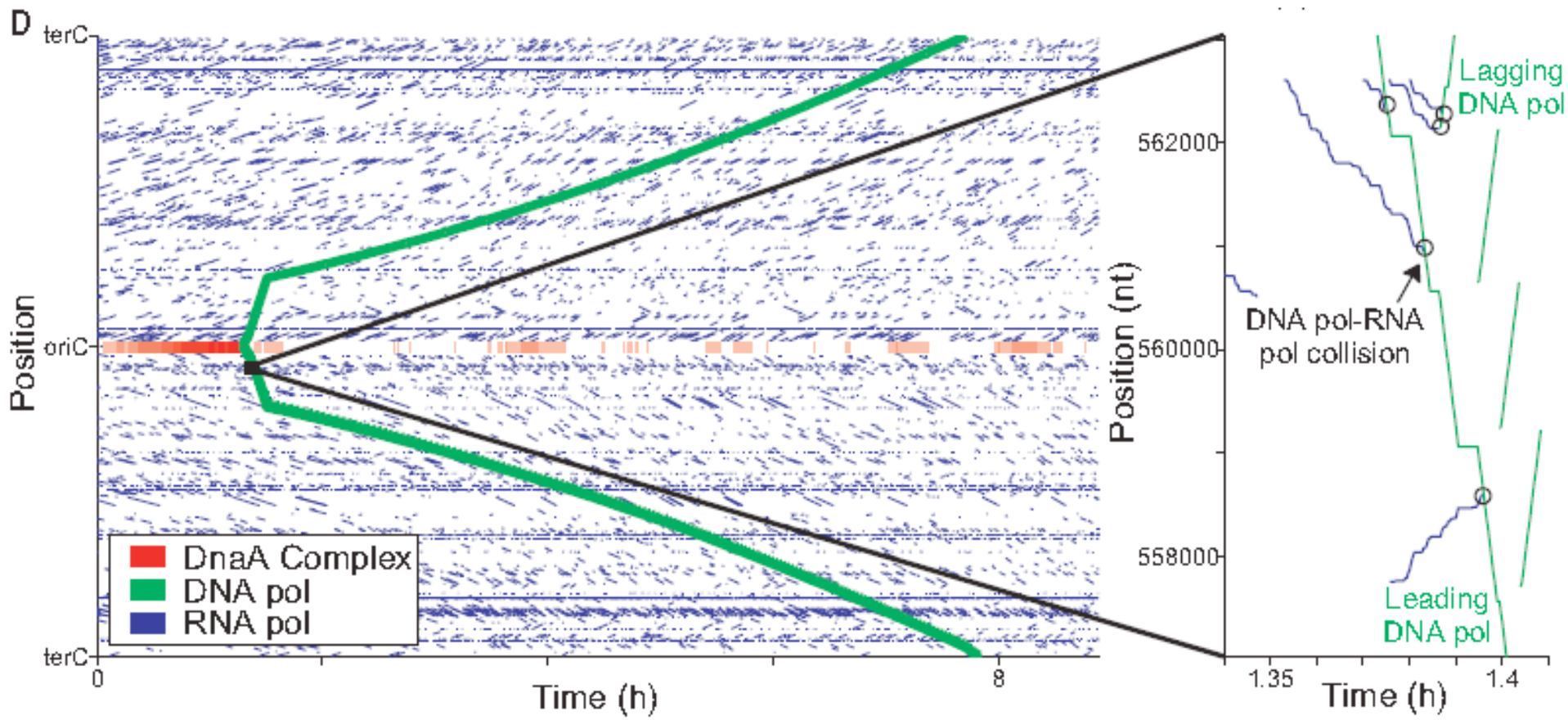
Growth of virtual cell culture



Growth of three cultures (dilutions indicated by shade of blue) and a blank control measured by OD550 of the pH indicator phenol red. The doubling time, t, was calculated using the equation at the top left from the additional time required by more dilute cultures to reach the same OD550 (black lines).

The model calculations were consistent with the observed doubling time!

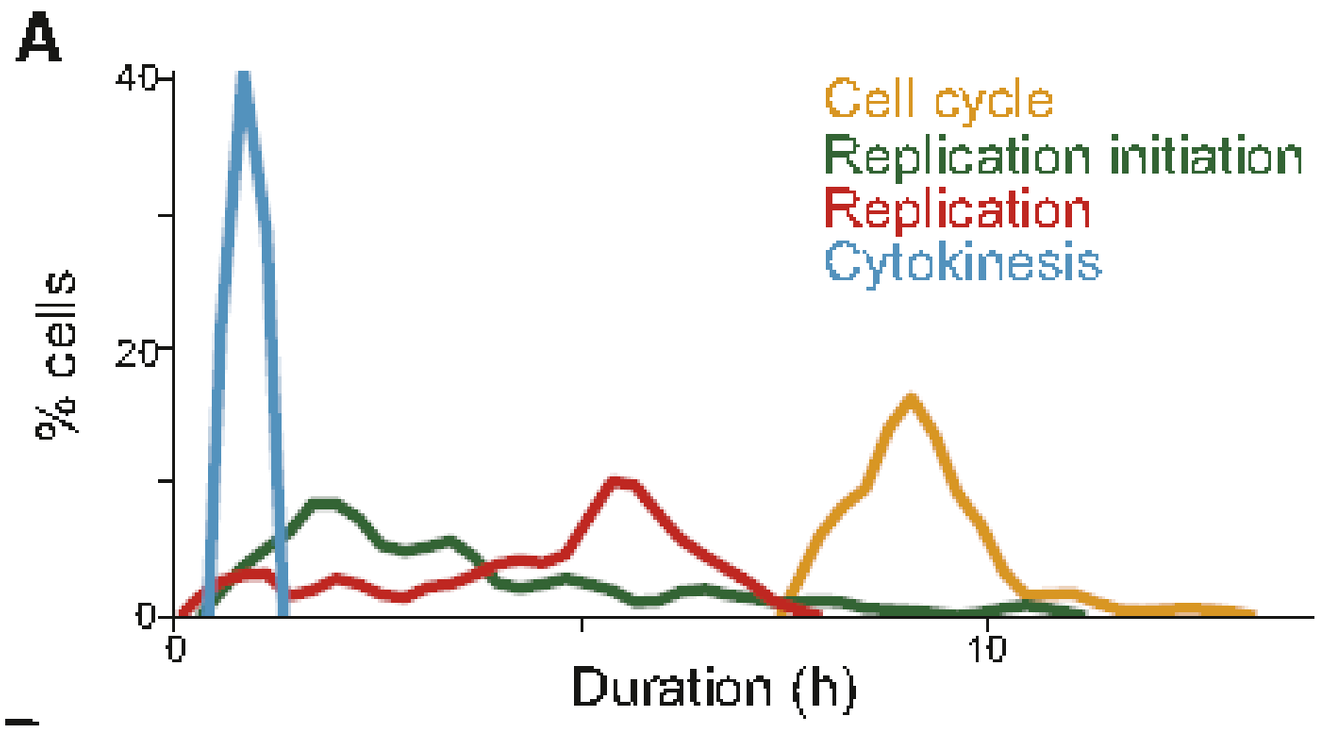
DNA-binding and dissociation dynamics



DNA-binding and dissociation dynamics of the oriC DnaA complex (red) and of RNA (blue) and DNA (green) polymerases for one in silico cell. The oriC DnaA complex recruits DNA polymerase to the oriC to initiate replication, which in turn dissolves the oriC DnaA complex. RNA polymerase traces (blue line segments) indicate individual transcription events. The height, length, and slope of each trace represent the transcript length, transcription duration, and transcript elongation rate, respectively.

Inset : several predicted collisions between DNA and RNA polymerases that lead to the displacement of RNA polymerases and incomplete transcripts.

Predictions for cell-cycle regulation

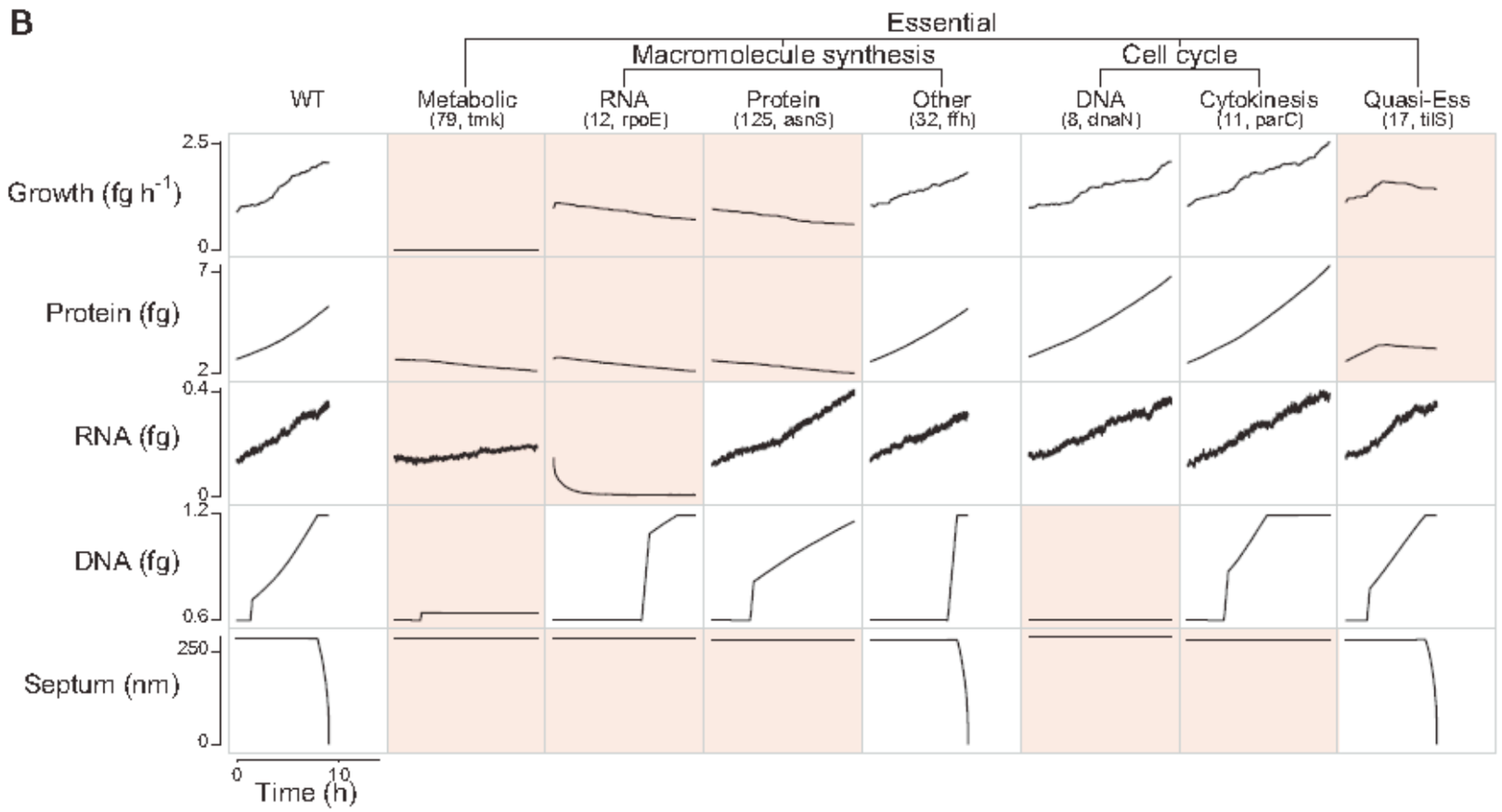


Distributions of the duration of three cell-cycle phases, as well as that of the total cell-cycle length, across 128 simulations.

There was relatively more cell-to-cell variation in the durations of the replication initiation (64.3%) and replication (38.5%) stages than in cytokinesis (4.4%) or the overall cell cycle (9.4%).

This data raised two questions:
(1) what is the source of duration variability in the initiation and replication phases; and
(2) why is the overall cell-cycle duration less varied than either of these phases?

Single-gene knockouts : essential vs. non-essential genes



Single-gene disruption strains grouped into phenotypic classes (columns) according to their capacity to grow, synthesize protein, RNA, and DNA, and divide (indicated by septum length).

Each column depicts the temporal dynamics of one representative in silico cell of each essential disruption strain class.

Dynamics significantly different from wild-type are highlighted in red.

The identity of the representative cell and the number of disruption strains in each category are indicated in parenthesis.

Literature

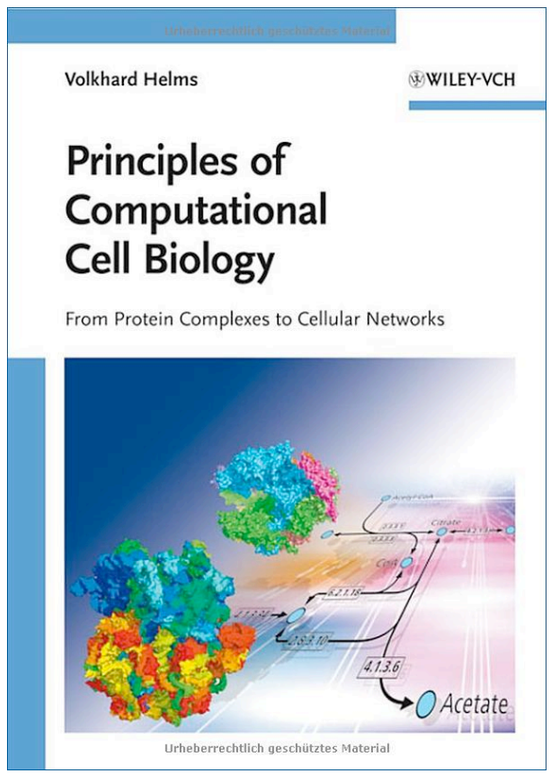
Lecture **slides** — available before the lecture

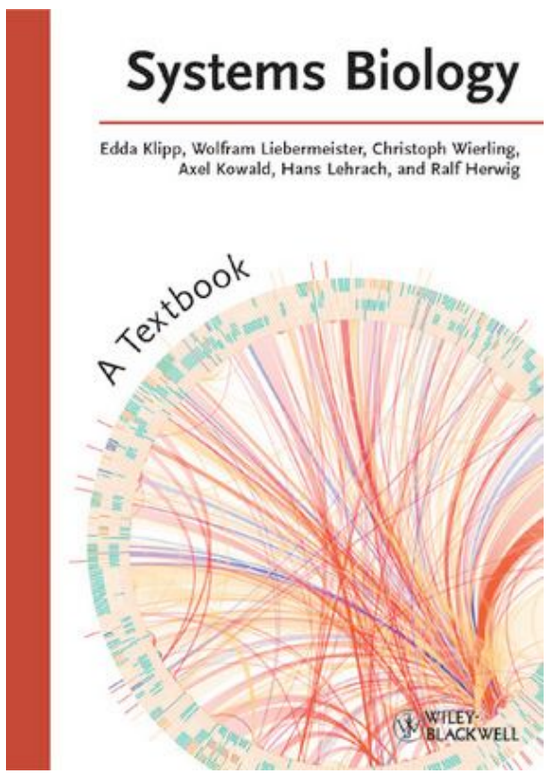
Suggested **reading**

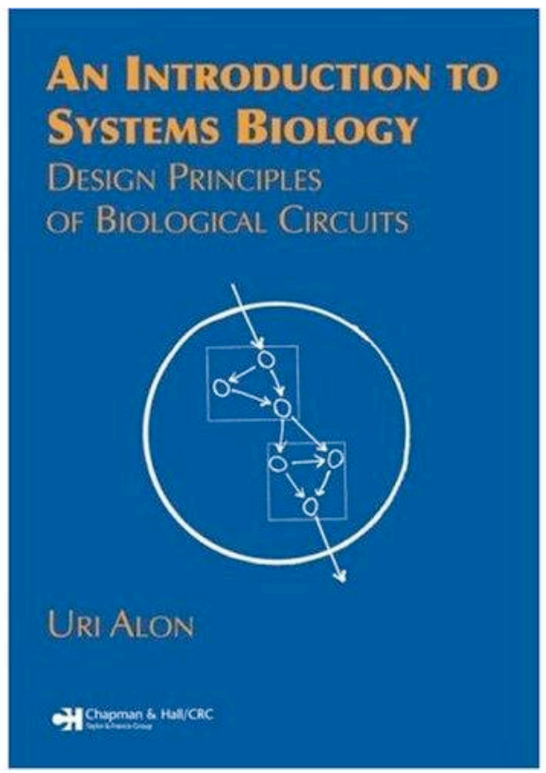
=> check our web page

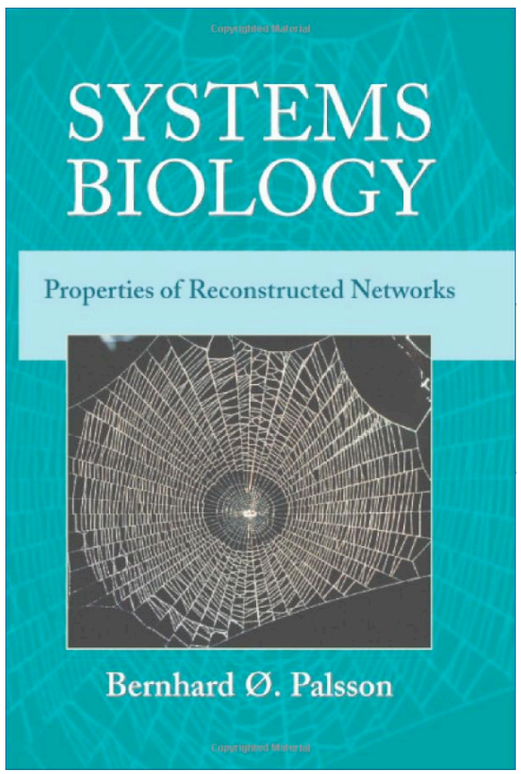
http://gepard.bioinformatik.uni-saarland.de/teaching/…

Textbooks









=> check computer science library

How to pass this course

Schein = you need to qualify for the the final exam and pass it

Final exam: written test of 180 min length about selected parts of the lecture (will be defined 2 weeks before exam) and about the assignments

requirements for participation:

- 50% of the points from the assignments
- one assignment task presented @ blackboard

Final exam will take place at the end of the semester

In case you are sick (final exam) you should bring a medical certificate to get a re-exam.

Re-exam: will take place in first week of the summer term 2016

Assignments

Tutors: Thorsten Will, Maryam Nazarieh
Duy Nguyen, Ha Vu Tranh

Tutorial: ?? Mon, 12:00–14:00, E2 1, room 007

10 assignments with 100 points each

Assignments are part of the course material (not everything is covered in lecture)

=> **one** solution for **two** students (or one)

=> hand-written or one **printable** PDF/PS file per email

=> content: data analysis + interpretation — **think!**

=> no 100% solutions required!!!

=> attach the source code of the programs for checking (no suppl. data)

=> present one task at the **blackboard**

Hand in at the following Fri electronically until 13:00 or
printed at the start of the lecture.

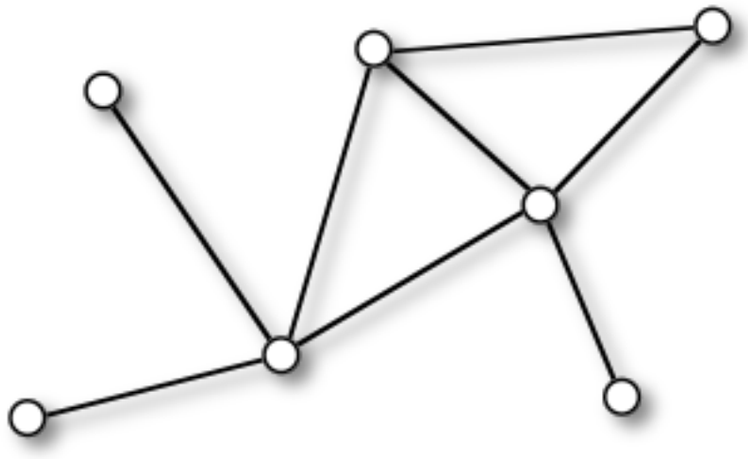
Some Graph Basics

Network <=> Graph

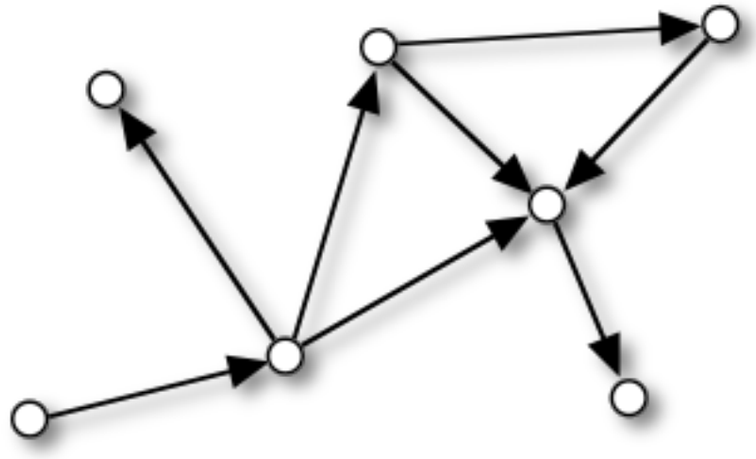
Formal **definition**:

A **graph** *G* is an ordered pair (*V, E*) of a set *V* of **vertices** and a set *E* of **edges**.

$$G = (V, E)$$



undirected graph



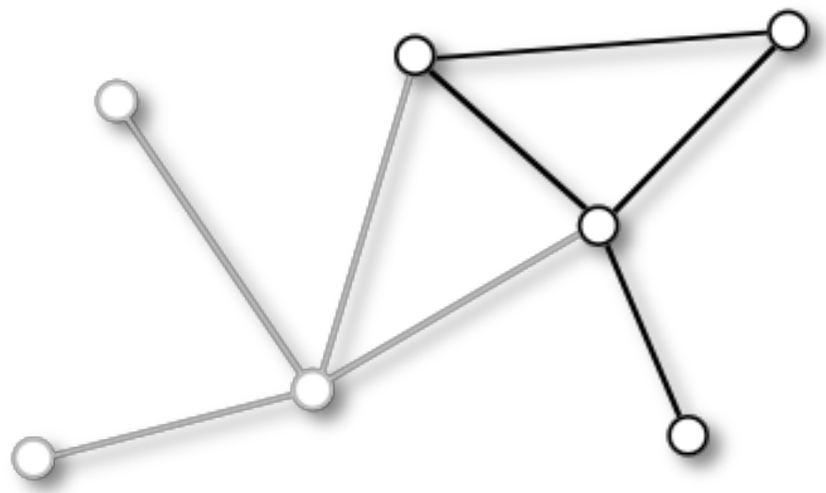
directed graph

If $E = V^{(2)}$ => fully connected graph

Graph Basics II

Subgraph:

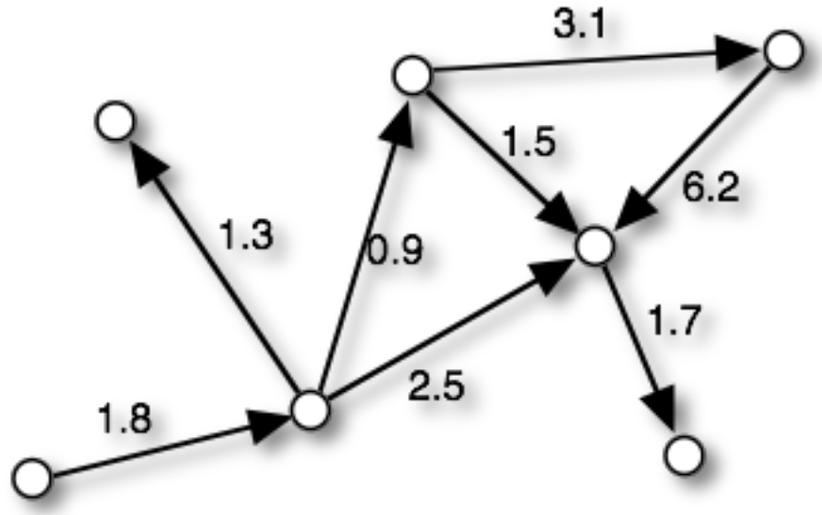
G' = (V', E') is a subset of *G = (V, E)*



Practical question: how to define useful subgraphs?

Weighted graph:

Weights assigned to the edges



Note: no weights for vertices

Walk the Graph

Path = sequence of connected vertices

start vertex => internal vertices => end vertex

Two paths are **independent** (internally vertex-disjoint),

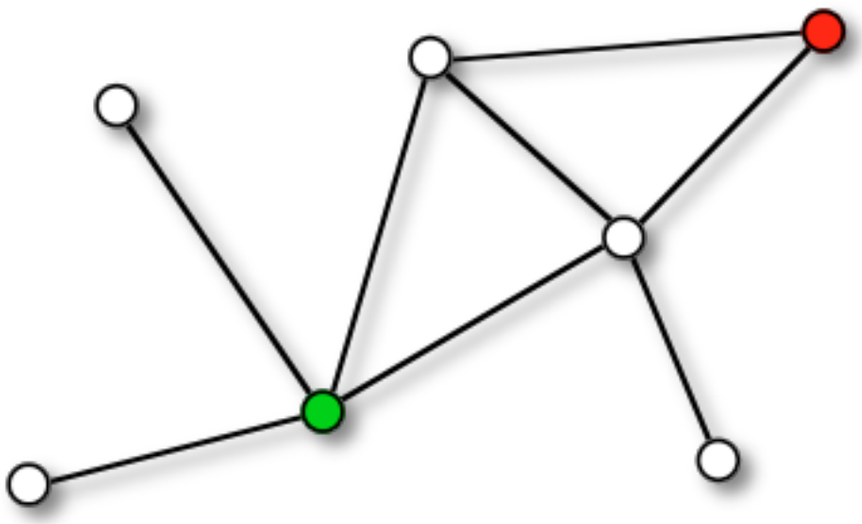
if they have no internal vertices in common.

Vertices *u* and *v* are **connected**, if there exists a path from *u* to *v*.

otherwise: disconnected

Trail = path, in which all edges are distinct

Length of a path = number of vertices || sum of the edge weights



How many paths connect the green to the red vertex?

How long are the shortest paths?

Find the four trails from the green to the red vertex.

How many of them are independent?

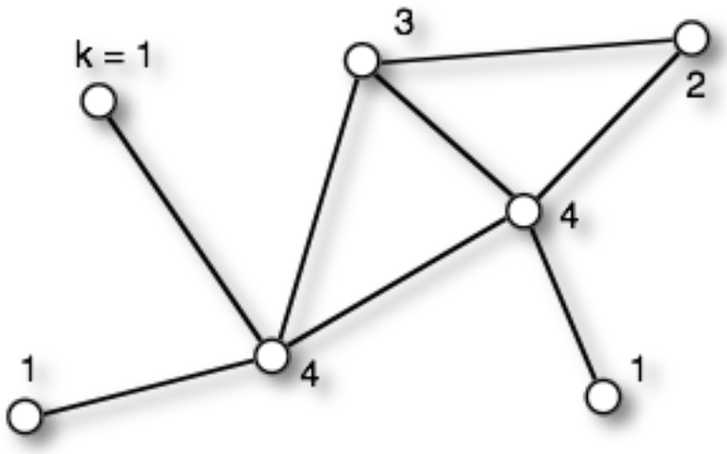
Local Connectivity: Degree/Degree Distribution

Degree *k* of a vertex = number of edges at this vertex

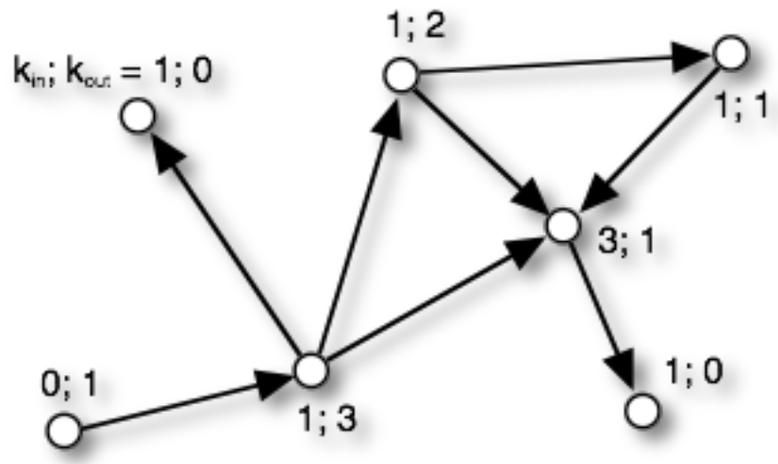
Directed graph => distinguish k_{in} and k_{out}

Degree distribution *P(k)* = fraction of nodes with *k* connections

$$P(k) = \frac{n_k}{N}$$



k	0	1	2	3	4
P(k)	0	3/7	1/7	1/7	2/7

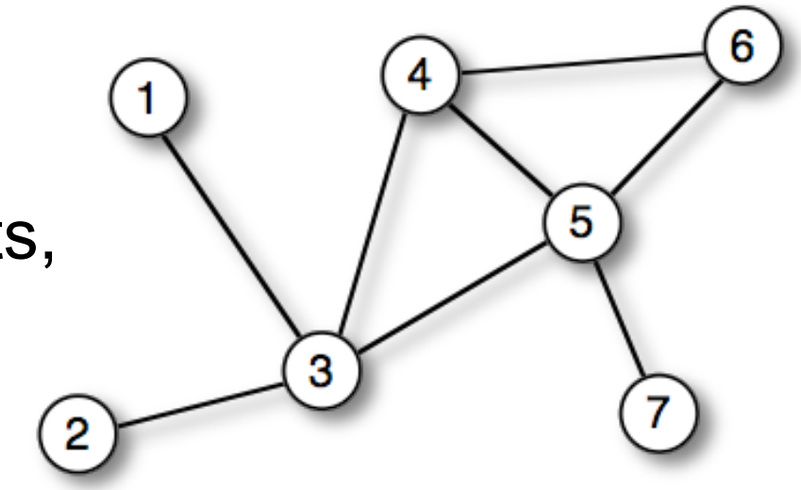


k	0	1	2	3
$P(k_{in})$	1/7	5/7	0	1/7
$P(k_{out})$	2/7	3/7	1/7	1/7

Graph Representation e.g. by adjacency matrix

Adjacency matrix is a *N* x *N* matrix
with entries M_{uv}

M_{uv} = weight when edge between *u* and *v* exists,
0 otherwise



→ symmetric for undirected graphs

+ fast *O(1)* lookup of edges
– large memory requirements
– adding or removing nodes is expensive

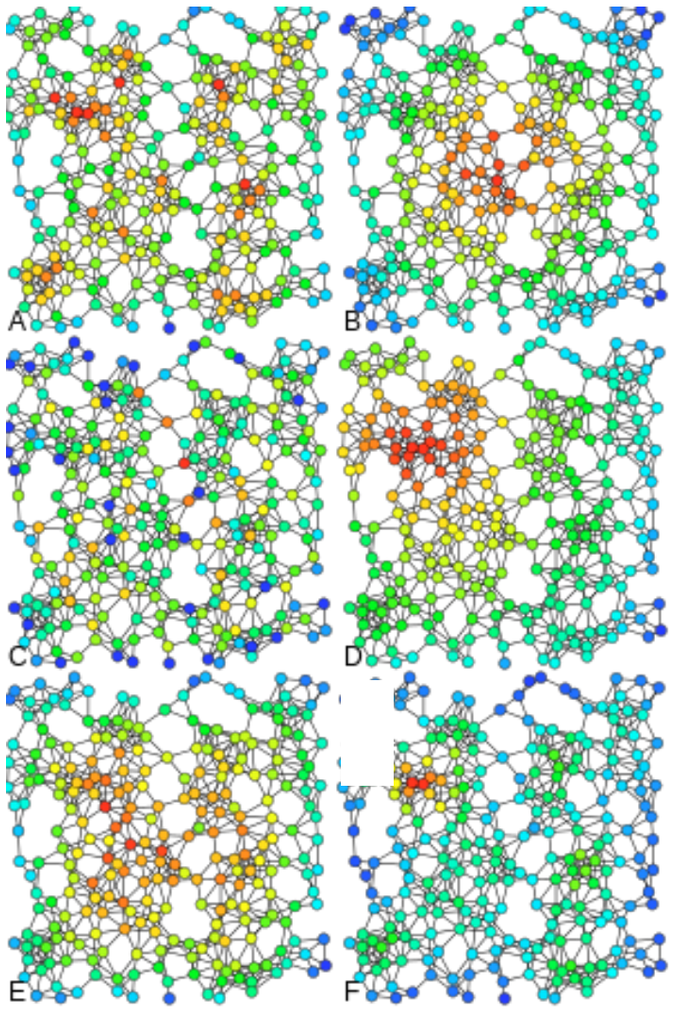
Note: very convenient in programming languages that support sparse multi-dimensional arrays
=> Perl

	1	2	3	4	5	6	7
1	–	0	1	0	0	0	0
2	0	–	1	0	0	0	0
3	1	1	–	1	1	0	0
4	0	0	1	–	1	1	0
5	0	0	1	1	–	1	1
6	0	0	0	1	1	–	0
7	0	0	0	0	1	0	–

Measures and Metrics

“ Which are the most important or central vertices in a network? “

Examples of
A) Degree centrality,



B) Closeness centrality,

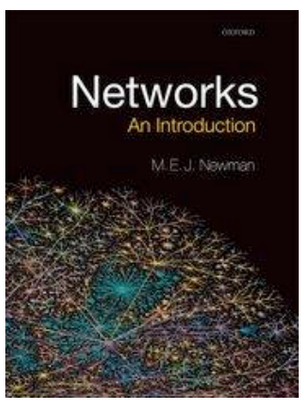
C) Betweenness centrality,

D) Eigenvector centrality,

E) Katz centrality,

F) Alpha centrality of the same graph.

www.wikipedia.org



book by Mark Newman / Oxford Univ Press

- Chapter 7: measures and metrics
- Chapter 11: matrix algorithms and graph partitioning

Degree centrality

Perhaps the simplest centrality measure in a network is the **degree centrality** that is simply equal to the **degree** of each vertex.

E.g. in a **social network**, individuals that have many connections to others might have

- more **influence**,
- more **access to information**,
- or more **prestige** than those individuals who have fewer connections.

A natural extension of the simple degree centrality is **eigenvector centrality**.

Towards Eigenvector Centrality

Let us start by defining the **centrality** of vertex x_i as the sum of the centralities of all its neighbors:

$$x_i' = \sum_j A_{ij} x_j$$

where A_{ij} is an element of the adjacency matrix.
(This equation system must be solved recursively until convergence.)

We can also write this expression in matrix notation as

$\mathbf{x'} = \mathbf{A}\,\mathbf{x}$ where $\mathbf{x}$ is the vector with elements x_i .

Repeating this process to make better estimates gives after t steps the following vector of centralities:

$$\mathbf{x}(t) = \mathbf{A}^t\,\mathbf{x}(0)$$

Eigenvector Centrality

Now let us write **x**(0) as a linear combination of the eigenvectors $\mathbf{v}_i$ of the (quadratic) adjacency matrix[1]

$$\mathbf{x}(0) = \sum_i c_i \mathbf{v}_i \qquad \text{with suitable constants } c_i$$

Then $\mathbf{x}(t) = A^t \sum_i c_i \mathbf{v}_i = \sum_i c_i \, {k_i}^t \, \mathbf{v}_i = {k_1}^t \sum_i c_i \left[\frac{k_i}{k_1}\right]^t \mathbf{v}_i$

where the k_i are the eigenvalues of **A** and k_1 is the largest of them.

(remember **A x** = λ **x** from linear algebra for each eigenvector **x**)

Since $k_i \,/\, k_1 < 1$ for all $i \neq j$, all terms in the sum decay exponentially as t becomes large.

In the limit $t \to \infty$, we get $\mathbf{x}(t) = c_1 \, {k_1}^t \, \mathbf{v}_1$

[1] Remember from linear algebra that a quadratic matrix with full rank can be diagonalized.

Eigenvector Centrality

This limiting vector of the eigenvector centralities is simply proportional to the leading eigenvector of the adjacency matrix.

Equivalently, we could say that the centrality **x** satisfies

$$\mathbf{A}\,\mathbf{x} = k_1\,\mathbf{x}$$

This is the **eigenvector centrality** first proposed by Bonacich (1987).

The centrality x_i of vertex *i* is proportional to the sum of the centralities of its neighbors:

$$x_i = {k_1}^{-1} \sum_j A_{ij} x_j$$

This has the nice property that the centrality can be large either because a vertex has many neighbors or because it has important neighbors with high centralities (or both).

Problems of the Eigenvector Centrality

The eigenvector centrality works best for undirected networks.

For directed networks, certain complications can arise.

In the figure on the right, vertex A will have eigenvector centrality zero.

Hence, vertex B will also have centrality zero.

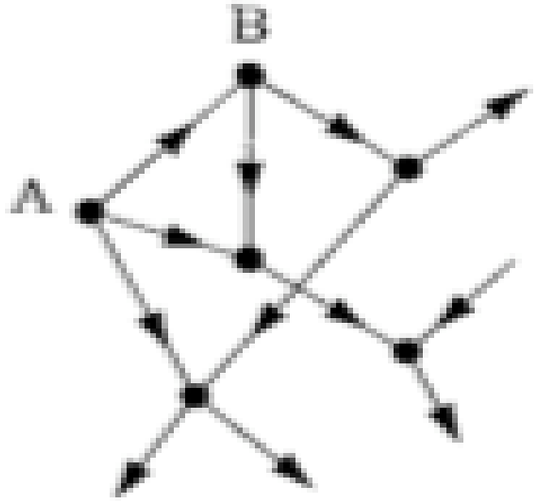


Figure 7.1: A portion of a directed network. Vertex A in this network has only outgoing edges and hence will have eigenvector centrality zero. Vertex B has outgoing edges and one ingoing edge, but the ingoing one originates at A, and hence vertex B will also have centrality zero.

Katz Centrality

One solution to the issues of the Eigenvector Centrality is the following:

We simply give each vertex a small amount of centrality “for free”,
regardless of its position in the network or the centrality of its neighbors.

→ we define $x_i = \alpha \sum_j A_{ij} x_j + \beta$ where α and β are positive constants.

In matrix terms, this can be written as $\mathbf{x} = \alpha\mathbf{A}\mathbf{x} + \beta\,\mathbf{1}$

where **1** is the vector $(1,1,1,\ldots)^T$. By rearranging for **x** we find

$$\mathbf{I}\,\mathbf{x} - \alpha\,\mathbf{A}\,\mathbf{x} = \beta\,\mathbf{1} \qquad \text{(where we used } \mathbf{I}\,\mathbf{x} = \mathbf{x}\text{)}$$
$$(\mathbf{I} - \alpha\,\mathbf{A})\,\mathbf{x} = \beta\,\mathbf{1}$$
$$(\mathbf{I} - \alpha\,\mathbf{A})^{-1}\,(\mathbf{I} - \alpha\,\mathbf{A})\,\mathbf{x} = (\mathbf{I} - \alpha\,\mathbf{A})^{-1}\,\beta\,\mathbf{1}$$
$$\mathbf{x} = \beta\,(\mathbf{I} - \alpha\,\mathbf{A})^{-1}\,\mathbf{1}$$

When setting β =1, we get the **Katz centrality** (1953) $\mathbf{x} = (\mathrm{I} - \alpha\,\mathbf{A})^{-1}\,\mathbf{1}$

Computing the Katz Centrality

The Katz centrality differs from the ordinary eigenvector centrality by having a **free parameter** α, which governs the balance between the eigenvector term and the constant term.

However, inverting a matrix on a computer has a complexity of $O(n^3)$ for a graph with n vertices.

This becomes prohibitively expensive for networks with more than 1000 nodes or so.

It is more efficient to make an initial guess of x and then repeat

$$\mathbf{x}' = \alpha \mathbf{A}\mathbf{x} + \beta \mathbf{1}$$

many times. This will converge to a value close to the correct centrality.

A good test for convergence is to make two different initial guesses and run this until the resulting centrality vectors agree within some small threshold.

Towards PageRank

The Katz centrality also has one feature that can be **undesirable**.

If a vertex with high Katz centrality has edges pointing to many other vertices, then all those vertices also get high centrality.

E.g. if a Wikipedia page points to my webpage,
my webpage will get a centrality comparable to Wikipedia!

But Wikipedia of course also points to many other websites,
so that its contribution to my webpage “should” be relatively small
because my page is only one of millions of others.

-> we will define a variation of the Katz centrality in which the centrality I derive from my network neighbors is proportional to their centrality divided by their out-degree.

PageRank

This centrality is defined by

$$x_i = \alpha \sum_j A_{ij} \frac{x_j}{k_j^{out}} + \beta$$

At first, this seems problematic if the network contains vertices with zero outdegree.

However, this can easily be fixed by setting $k_j^{out} = 1$ for all such vertices.

In matrix terms, this equation becomes

$$\mathbf{x} = \alpha\, \mathbf{A}\, \mathbf{D}^{-1}\, \mathbf{x} + \beta\, \mathbf{1}$$

where **1** is the vector $(1,1,1,\ldots)^T$ and **D** the diagonal matrix with $D_{ij} = max(k_j^{out}, 1)$

PageRank

By rearranging we find that

$$\mathbf{x} = \beta\,(\mathbf{I} - \alpha\,\mathbf{A}\,\mathbf{D}^{-1})^{-1}\,\mathbf{1}$$

Because β plays the same unimportant role as before, we will set $\beta = 1$.

Then we get $\mathbf{x} = (\mathbf{I} - \alpha\,\mathbf{A}\,\mathbf{D}^{-1})^{-1}\,\mathbf{1} = \mathbf{D}\,(\mathbf{D} - \alpha\,\mathbf{A})^{-1}\,\mathbf{1}$

This centrality measure is commonly known as **PageRank**,
using the term used by Google.

PageRank is one of the ingredients used by Google
to determine the ranking of the answers to your queries.

α is a free parameter and should be chosen less than 1. (Google uses 0.85).

Hubs and Authorities

So far we have considered measures that assign high centrality to a vertex if those vertices that point to it have high centrality too.

However, in some networks it is appropriate also to accord a vertex high centrality if it **points** to others with high centrality.

E.g. a review article pointing at many important papers in one research field may be a useful source of information.

Authorities are nodes that contain useful information on a topic of interest.

Hubs are nodes that tell us where the best authorities can be found.

An authority may also be a hub, and vice versa.

Hubs and Authorities

Kleinberg developed this into a centrality algorithm called Hyperlink-induced topic search (HITS).

The HITS algorithm gives each vertex *i* in a network an **authority centrality** x_i and a **hub centrality** y_i .

A vertex with high authority centrality is pointed to by many hubs, i.e. by many other vertices with high hub centrality.

A vertex with high hub centrality points to many vertices with high authority centrality.

Thus, an important scientific paper (in the authority sense) would be one that is cited in many important reviews (in the hub sense).

An important review is one that cites many important papers.

Authority and Hub Centralities

Kleinberg defined the **authority centrality** of a vertex to be proportional to the sum of the hub centralities of the vertices that point to it

$x_i = \alpha \sum_j A_{ij} y_j$ where α is a constant.

Similarly the **hub centrality** of a vertex is proportional to the sum of the authority centralities of the vertices it points to:

$y_i = \beta \sum_j A_{ji} x_j$ with another constant β

Note that the indices of the matrix element A_{ji} are swapped around in this second equation.

These equations can be written as $\mathbf{x} = \alpha\, \mathbf{A}\, \mathbf{y}$ and $\mathbf{y} = \beta\, \mathbf{A}^t\, \mathbf{x}$

Or, combining the two, $\mathbf{A}\, \mathbf{A}^t\, \mathbf{x} = \lambda\, \mathbf{x}$, $\mathbf{A}^t\, \mathbf{A}\, \mathbf{y} = \lambda\, \mathbf{y}$

Closeness centrality

An entirely different measure of centrality is provided
by the **closeness centrality.**

Suppose d_{ij} is the length of a geodesic path (i.e. the shortest path)
from a vertex *i* to another vertex *j*.
Here, length means the number of edges along the path.

Then, the mean **geodesic distance** from *i,* averaged over
all vertices *j* in the network is

$$l_i = \frac{1}{n}\sum_j d_{ij}$$

The mean distance l_i is not a centrality measure in the same sense
as the other centrality measures.

It gives *low* values for more central vertices and
high values for less central ones.

Closeness centrality

The inverse of l_i is called the **closeness centrality** C_i

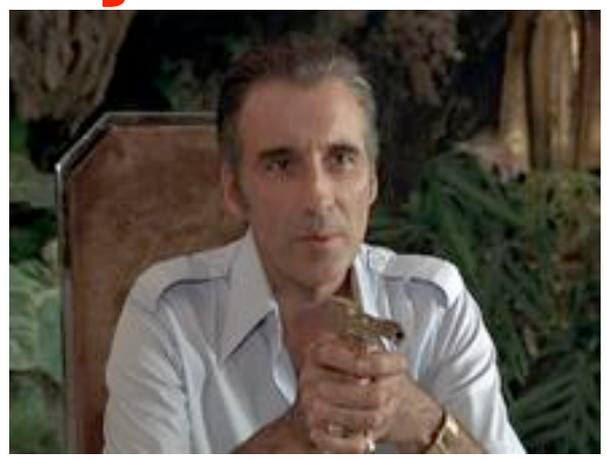
$$C_i = \frac{1}{l_i} = \frac{n}{\sum_j d_{ij}}$$

It has become popular in recent years to rank **film actors** according to their closeness centrality in the network of who has appeared in films with who else.

Using data from www.imdb.com the largest component of the network includes more than 98 % of about half a million actors.

Closeness centrality

The highest closeness centrality of any actor is 0.4143 for Christopher Lee.



The second highest centrality has Donald Pleasence (0.4138).

The lowest value has the Iranian actress Leia Zanganeh (0.1154).

→ the closeness centrality values are crammed in a very small interval [0,0.4143]

Other centrality measures including degree centrality and eigenvector centrality typically don‘t suffer from this problem. They have a wider dynamic range.

Pictures from wikipedia

Summary

What you learned **today**:

=> **networks** are everywhere

$\Rightarrow$ how to get the "**Schein**" for BI3

$\Rightarrow$ How to determine the most central nodes in a network

Next lecture:

=> basic network **types** and **definitions**:

random, scale-free, degree distribution, Poisson distribution, ageing, …

=> clusters, percolation

=> algorithm on a graph: Dijkstra's shortest path algorithm

=> looking at graphs: graph layout