Architecture of Randomly Evolving Idiotypic Networks

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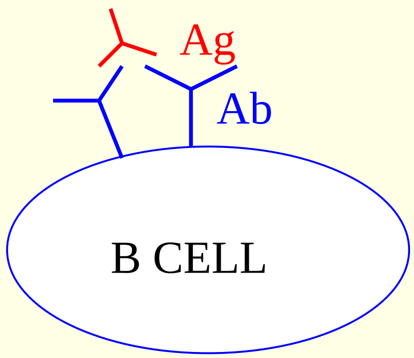
- B-lymphocytes, antibodies, idiotypic networks
- Bit chain model and dynamical rules
- Random evolution of the network
- Understanding the architecture
- Outlook

M. Brede, U.B., Phys. Rev. E **67**, 031920 (2003)

H. Schmidtchen, U.B., Proc. ECMTB 2005 (Birkhäuser, in press)

The B-Lymphocyte System

- B-lymphocytes express highly specific receptors on their surface: antibodies of a given idiotype.

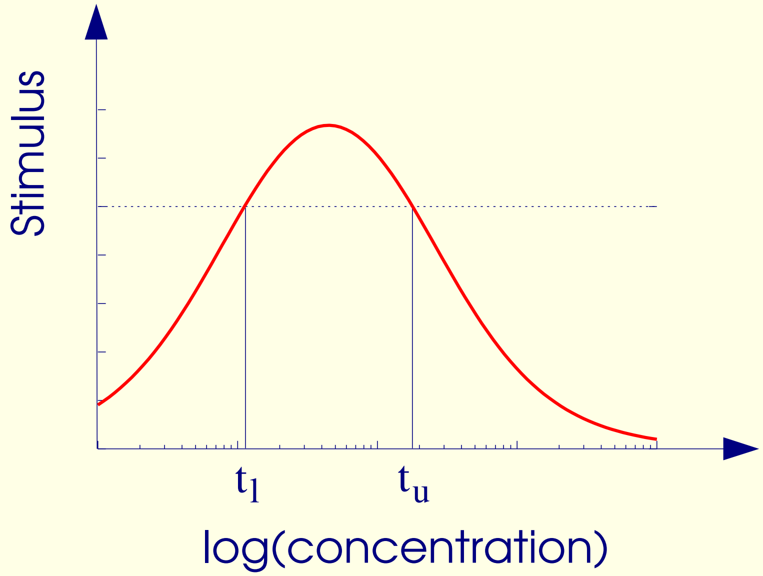


- Stimulation if receptors are crosslinked by complementary structures

- **Clonal Selection (Burnett, 1959)**

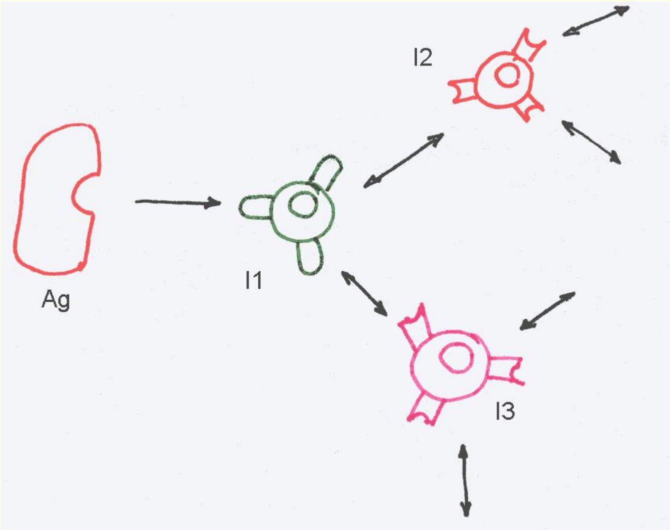
  B-lymphocytes of random specifity are produced by mutations in the bone marrow.

  Stimulated B-lymphocytes proliferate and secrete usefull antibodies – the others die



Idiotypic Networks (Jerne, 1974)

- Network of complementary idiotypes
- Antigen independent dynamics driven by new idiotypes
- Memory: internal images of antigen
- Repertoire of idiotypes: potential 10^{12} vs expressed 10^{7}



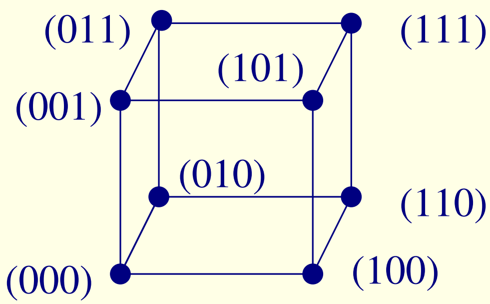
Architecture (Coutinho, 1989): Completeness vs memory
Central Part (highly connected) vs Peripheral Part (isolated)
Architecture changes in an individual's life

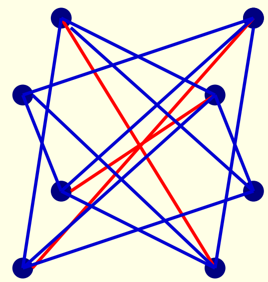
The Bitstring Model

Complementary structures are characterized by bitstrings

Idiotype	$(0\|1\|1\|1\|0\|1\|0\|0\|1\|1\|0\|0)$	Length d
Complementary idiotype	$(1\|0\|0\|0\|1\|1\|1\|1\|0\|0\|1\|1)$	Allowed mismatches m

$d = 3$
Hypercube





Base graph $G_d^{(m)}$
$m = 1$

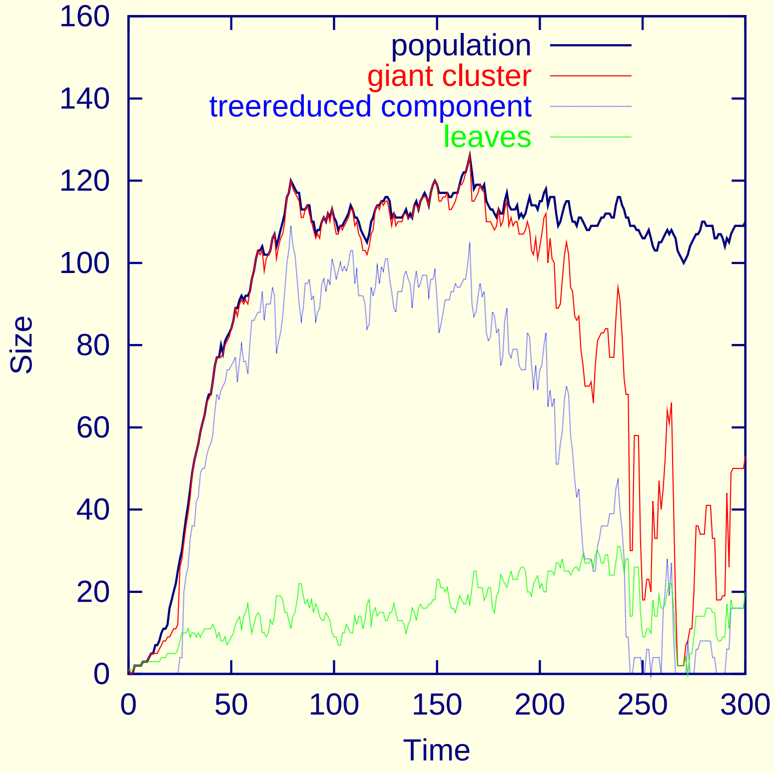
The nodes of the base graph can be occupied (1) or empty (0)

Update algorithm:

(i) Random influx: Occupy randomly I empty vertices
(ii) Population dynamics: Remove occupied vertices if the number of occupied neighbors is outside (t_l, t_u)
(iii) Iterate

Simulation Results: Typical Course of Evolution

Time series of simulations on $G_{12}^{(1)}$ with $(t_l, t_u) = (1, 7)$ for $I = 10$:



(i) Formation of germs

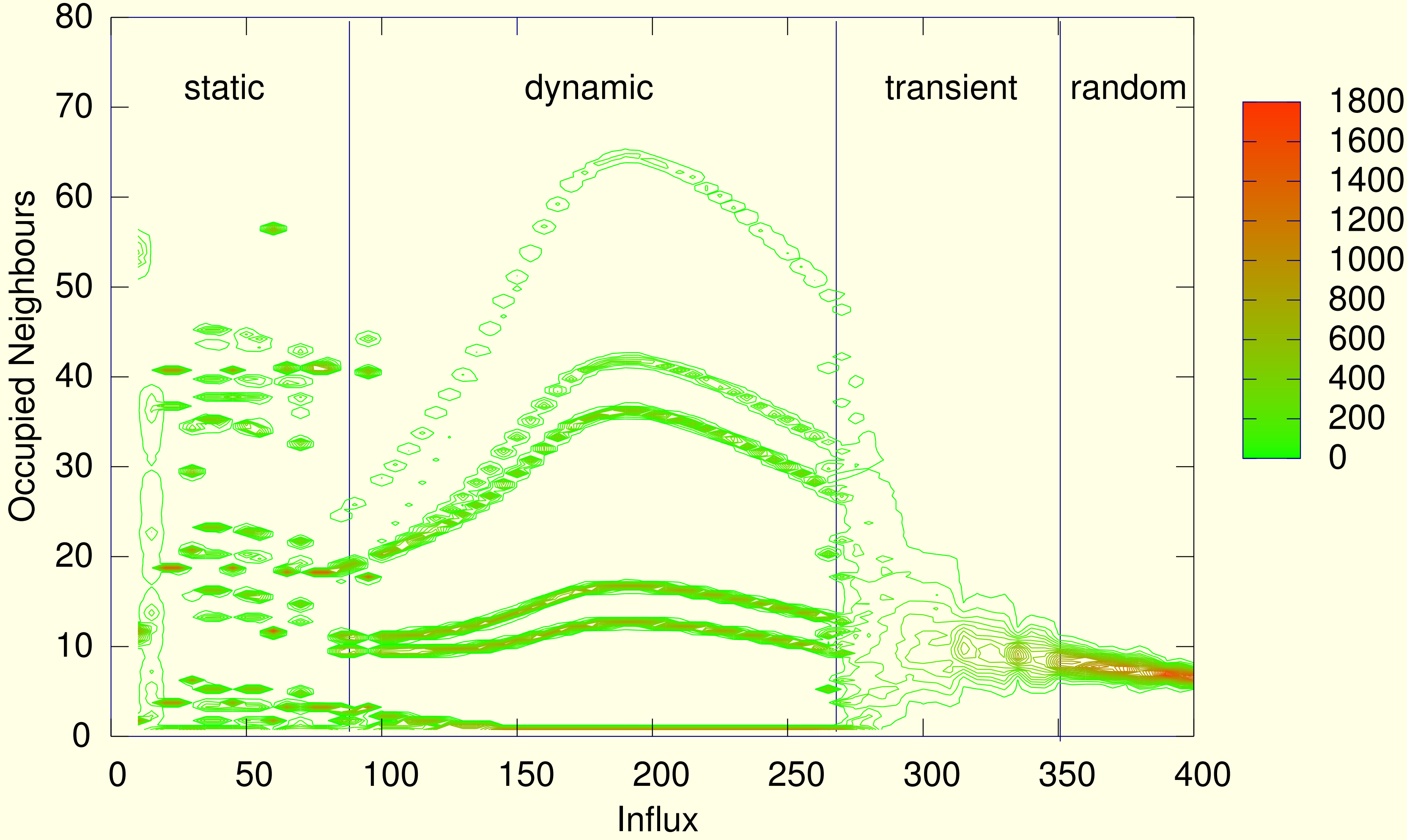
(ii) Almost linear growth of population

(iii) Formation of a giant cluster

(iv) Breakdown of the giant cluster

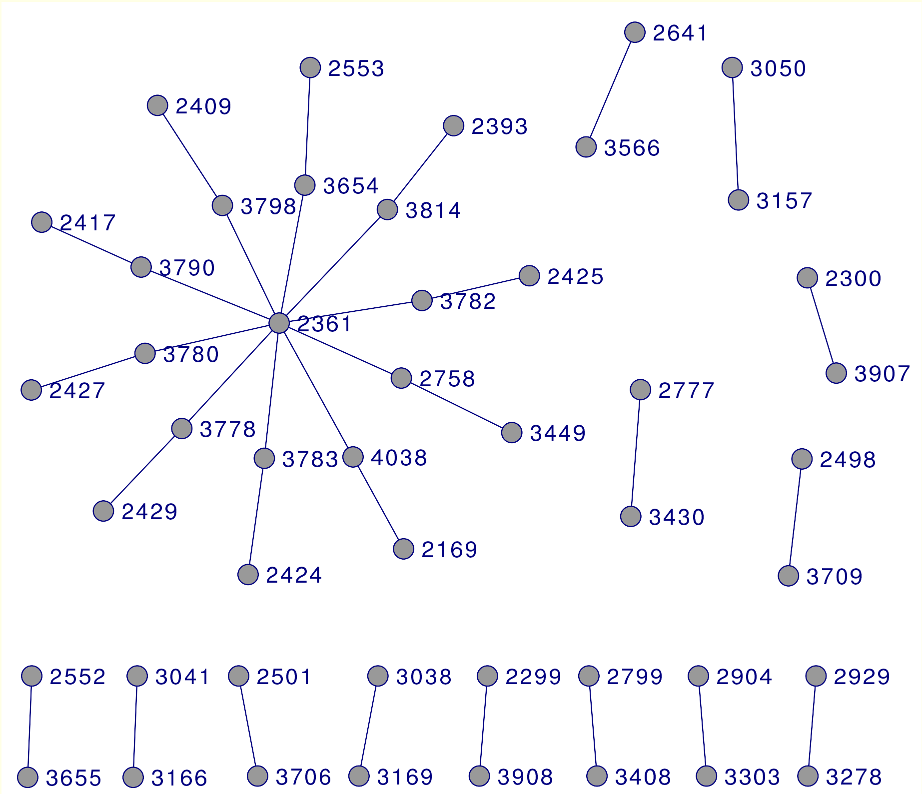
(v) Reorganization, steady state

Simulation Results: Number of Occupied Neighbors



Simulations on $G_{12}^{(2)}$ for $(t_l, t_u) = (1, 10), (T_0, T_1) = (5000, 10000)$

Simulation Results: 2-Cluster Pattern with Hubs



Simulations on $G_{12}^{(2)}$
$(t_l, t_u) = (1, 10)$
for $I = 10$

Index sum of 2-clusters is constant:

$$\begin{array}{rr} & 2641 \\ + & 3566 \\ \hline & 6207 \end{array}$$

3 groups of nodes $\mathbf{S_i}$

		2-Clusters (S_1)	Hubs (S_2)	Holes (S_3)
Occupied neighbors	$\langle \overline{n(\partial v)} \rangle_{S_i}$	1.16	10.96	53.26
Mean life time	$\langle \overline{\tau(v)} \rangle_{S_i}$	4699	3	0
Mean occupation	$\langle \overline{n(v)} \rangle_{S_i}$	0.95	0.01	0.00

Combinatorial Description of the 2-Cluster Pattern

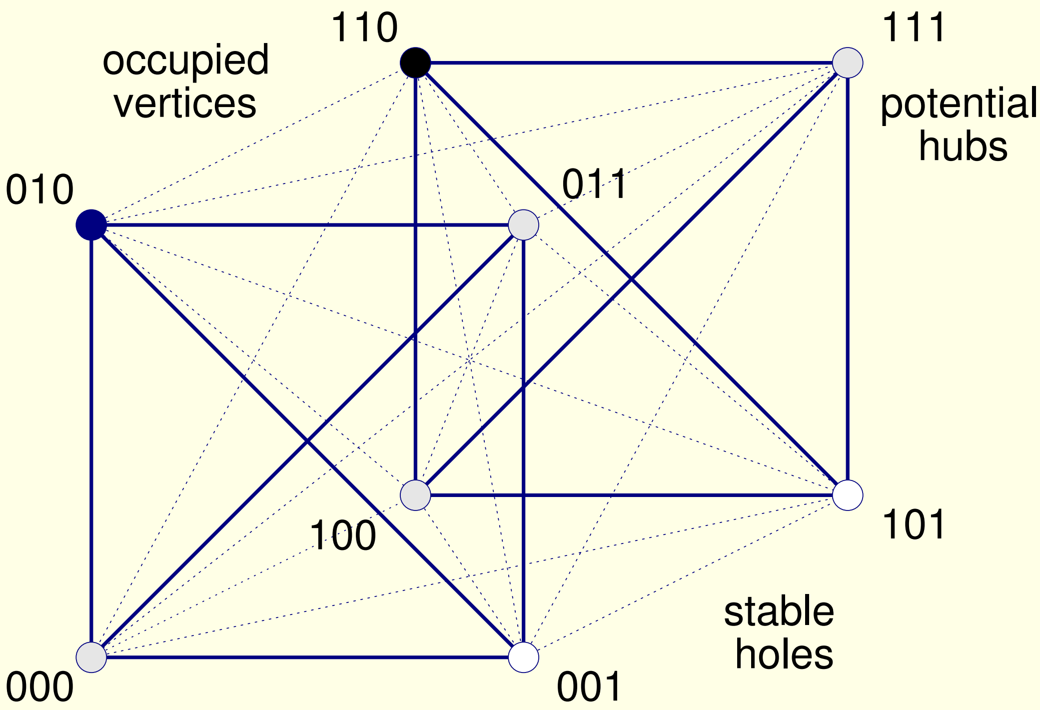
All nodes of 2-clusters on $G_d^{(2)}$ have two determinant bits in common:

2-clusters	S_1	$\bullet\bullet\bullet\, \boldsymbol{b_k}\, \bullet\bullet\bullet\, \boldsymbol{b_l}\, \bullet\bullet\bullet\bullet$ $\overline{\bullet\bullet\bullet}\, \boldsymbol{b_k}\, \overline{\bullet\bullet\bullet}\, \boldsymbol{b_l}\, \overline{\bullet\bullet\bullet\bullet}$
stable holes	S_3	$\circ\circ\circ\, \overline{\boldsymbol{b_k}}\, \circ\circ\circ\, \overline{\boldsymbol{b_l}}\, \circ\circ\circ\circ$
potential hubs	S_2	$\bullet\, \overline{\bullet}\, \bullet\, \overline{\boldsymbol{b_k}}\, \bullet\bullet\bullet\, \boldsymbol{b_l}\, \bullet\bullet\bullet\bullet$

The number of occupied neighbors of a node in S_i is $n(\partial v) = \sum_{j=0}^{i-1} \binom{d-2}{j}$

$n(\partial v)$	S_1	S_2	S_3
Combinatorics	1	11	56
Simulation	1.16	10.96	53.26

The Pattern Module of the 2-Cluster Pattern on $G_d^{(2)}$



$G_3^{(2)}$
$(t_l, t_u) = (1, 1)$

The pattern module comprises nodes with identical non-determinant bits (here the first bit).

The two determinant bits encode the nodes of the module.

Congruently occupied, repeating modules are the building blocks of the pattern.

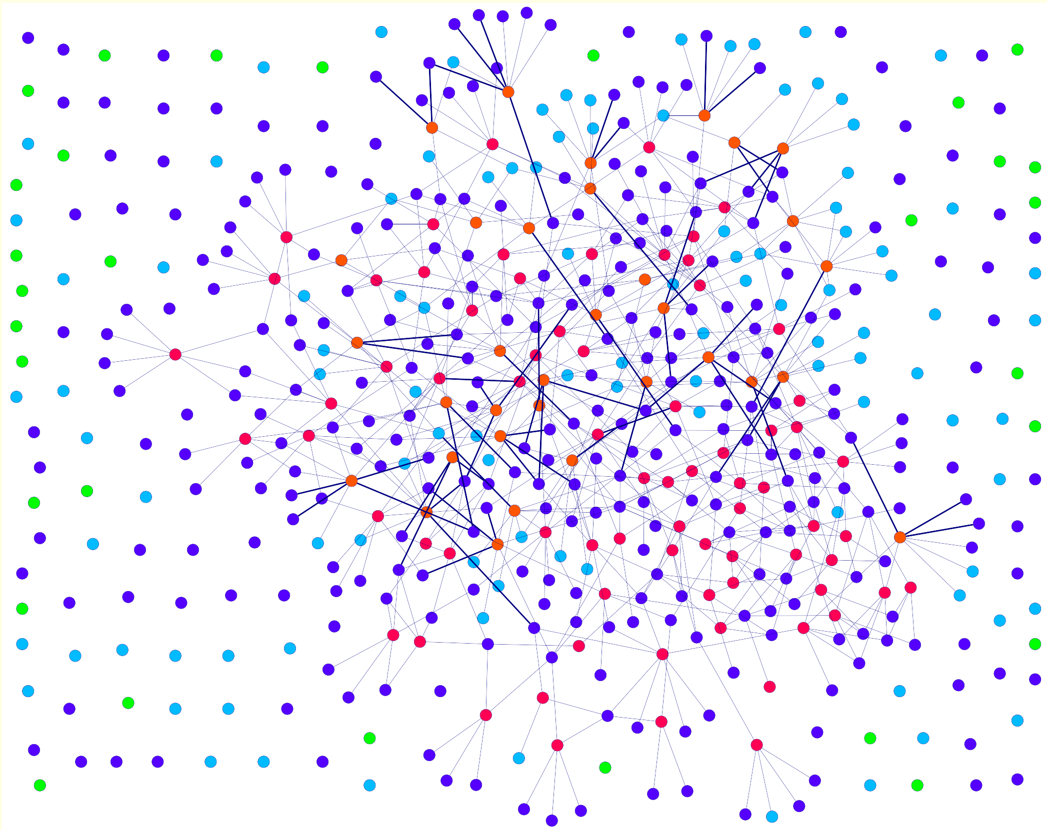
Generalizations

The concept of pattern modules easily allows generalization to other choices of the parameters d, m and to more complex patterns.

Given the number of determinant bits $d_M < d$ we can calculate the number of groups, their relative sizes, and their interconnectivity.

d_M	Relative size of different groups	Observed pattern on $G_{12}^{(2)}$
0	1	
1	1 1	
2	**1** 2 1	2-cluster pattern
3	**1** **3** 3 1	24-cluster pattern
4	1 **4** 6 4 1	8-cluster pattern
5	1 5 10 10 5 1	
6	1 6 **15** 20 15 6 1	30-cluster pattern
...	...	...

Simulation Results: Dynamic Six-group Pattern on $G_{12}^{(2)}$

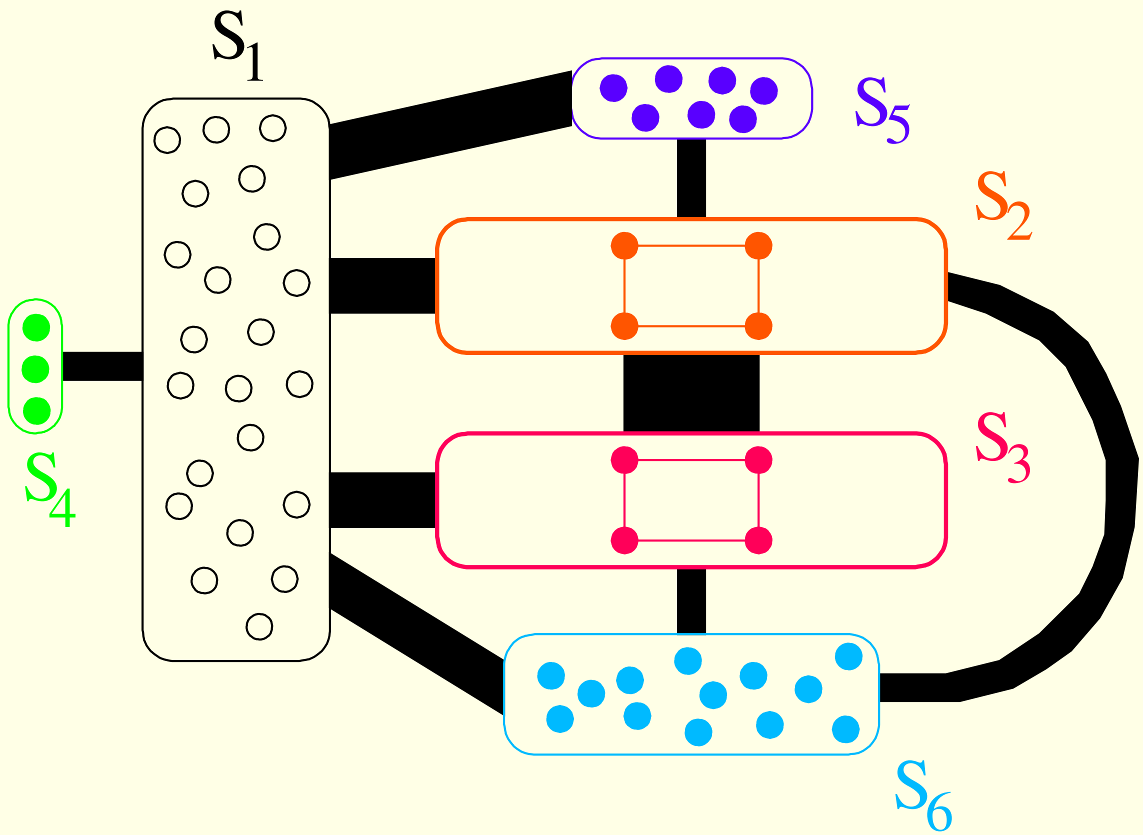


- S_1 — stable holes
- S_2, S_3 — core groups
- S_4 — isolated vertices
- S_5, S_6 — peripheral groups

$(t_l, t_u) = (1, 10)$
$I = 90$

		S_1	S_2	S_3	S_4	S_5	S_6
Group size	$\lvert S_i \rvert$	1124	924	924	134	330	660
Life time	$\langle \overline{\tau(v)} \rangle_{S_i}$	0.0	3.8	5.4	10.0	18.1	35.6

Group structure of the Dynamic Six-group Pattern



The size of the boxes corresponds to the group size. The lines show possible connections between vertices of the groups and their thickness is a measure of the number of connections.

Combinatorics of the Six-group Pattern

The structure of the six-group pattern can be explained considering an 11-dimensional pattern module. (Group S_1 has 5 subgroups and group S_4 has 3 subgroups which gives together 12 groups.)

By combinatorics we can determine the group size and the linking between the groups.

The **group sizes** are given by

$$|S_i| = 2^{d-d_M}\binom{d_M}{i-1}$$

	S_1	S_2	S_3	S_4	S_5	S_6	S_7	S_8	S_9	S_{10}	S_{11}	S_{12}
Group size	2	22	110	330	660	924	924	660	330	110	22	2
Empirical group	$\widetilde{S}_4$	$\widetilde{S}_4$	$\widetilde{S}_4$	$\widetilde{S}_5$	$\widetilde{S}_6$	$\widetilde{S}_3$	$\widetilde{S}_2$	$\widetilde{S}_1$	$\widetilde{S}_1$	$\widetilde{S}_1$	$\widetilde{S}_1$	$\widetilde{S}_1$

$\underbrace{S_1 \; S_2 \; S_3}_{134}$ $\qquad$ $\underbrace{S_8 \; S_9 \; S_{10} \; S_{11} \; S_{12}}_{1124}$

These are *exactly* the measured group sizes.

Linking between groups

The possible links between nodes of different groups are constraint by the allowed number of mismatches.

$$
\begin{array}{lcccccccccc}
v_i: & \bar{\boldsymbol{b}}_{k_1} & \bar{\boldsymbol{b}}_{k_2} & \dots & \bar{\boldsymbol{b}}_{k_{i-1}} & \boldsymbol{b}_{k_i} & \dots & \dots & \dots & \dots & \boldsymbol{b}_{k_{d_M}} \\
v_j: & \boldsymbol{b}_{k_1} & \boldsymbol{b}_{k_2} & \dots & \dots & \dots & \dots & \boldsymbol{b}_{k_{d_M-j+1}} & \bar{\boldsymbol{b}}_{k_{d_M-j+2}} & \dots & \bar{\boldsymbol{b}}_{k_{d_M}}
\end{array}
$$

$\underbrace{\qquad}_{i-1 \text{ bits}}$ $\underbrace{\qquad}_{m_{ij}^{\min}:=d_M-i-j+2 \text{ bits}}$ $\underbrace{\qquad}_{j-1 \text{ bits}}$

Combinatorics gives the number of links of a vertex of S_i to vertices of S_j as

$$
\sum_{k=0}^{k'} \sum_{l=0}^{l'} \binom{i-1}{k+\max(0, m_{ij}^{\min})} \binom{d_M-i+1}{k+\max(0, -m_{ij}^{\min})} \binom{d-d_M}{l},
$$

where $k' = [(m - |m_{ij}^{\min}|)/2]$, $l' = m - |m_{ij}^{\min}| - 2k$

Number of links of a node of S_i to nodes of S_j

	S_1	S_2	S_3	S_4	S_5	S_6
S_1	0	12,3	16,4	9,4	15	25,8
S_2	15	12	32	0	10	10
S_3	20	32	12	0	0	15
S_4	79	0	0	0	0	0
S_5	51	28	0	0	0	0
S_6	44	14	21	0	0	0

These combinatorical results agree *exactly* with the simulations (by M. Brede, PhD thesis 2003).

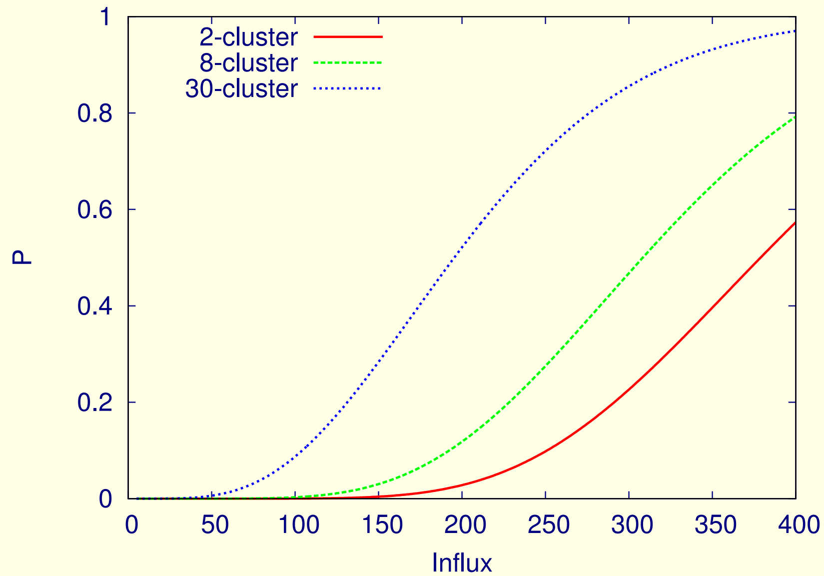
Note that the real patterns are dynamic.

Stability of Static Patterns

The probability for deletion of an occupied node v_0 in a perfect static pattern due to the random influx within one time step:

$$P[\Delta n(\partial v_0) \geq t_u + 1 - n(\partial v_0)] = \sum_{k=t_u+1-n(\partial v_0)}^{\min(f,I)} \frac{\binom{f}{k}\binom{F-f}{I-k}}{\binom{F}{I}},$$

where f is the number of holes in v_0's neighborhood, and F is the number of holes on the graph.



Summary

We achieved a detailed microscopic understanding of the building principles of the emerging complex architecture of a randomly evolving network.

The architecture displays many features of the biological network.

The concept of pattern modules allows many analytical results in excellent agreement with simulations.

Outlook

Stability of patterns, transitions, ergodicity breaking

Mean field description of the dynamics

Scaling to realistic network sizes applying renormalization group

More realistic models (multiple degrees of occupation, weighted links)

Co-evolution with a growing antigen

References

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- yEd - Java™ Graph Editor v2.3.1, `http://www.yWorks.com`