

Architecture of Randomly Evolving Idiotypic Networks

Holger Schmidtchen and Ulrich Behn

Institute of Theoretical Physics

International Max Planck Research School 'Mathematics in the Sciences'

University of Leipzig

-
- B-lymphocyte system and idiotypic networks
 - Bit chain model and dynamical rules
 - Random evolution of the network
 - Understanding the architecture
 - Mean field theory
 - Summary and outlook
-

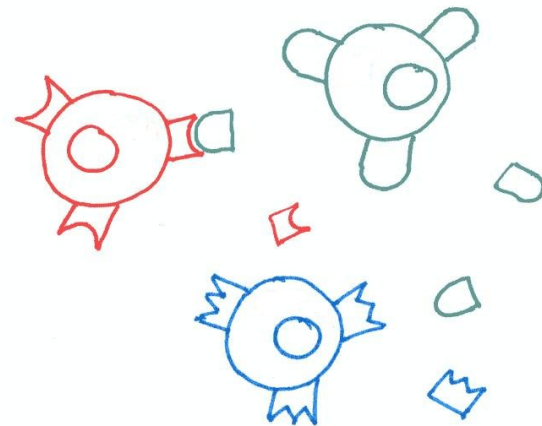
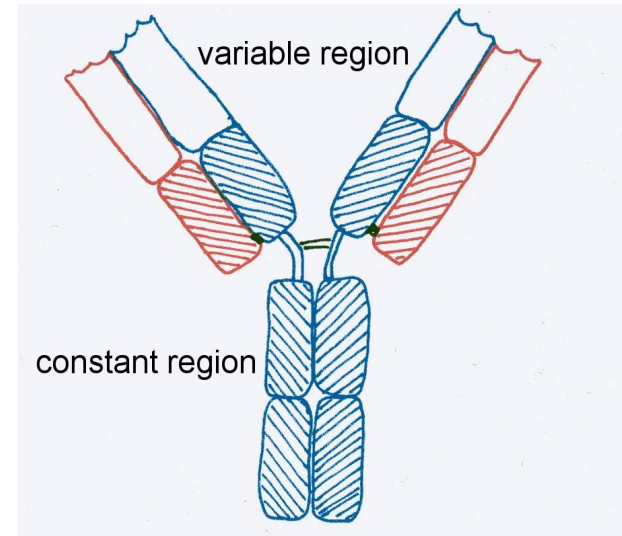
¹M. Brede, U.B., Phys. Rev. E **67**, 031920 (2003)

²H.S., U.B., Math. Modeling of Biol. Syst., Vol. II (Birkhäuser, 2007), 163–174, to appear

³H.S., U.B., LN Comp. Sci. **4163** (Springer, 2006), 81–94

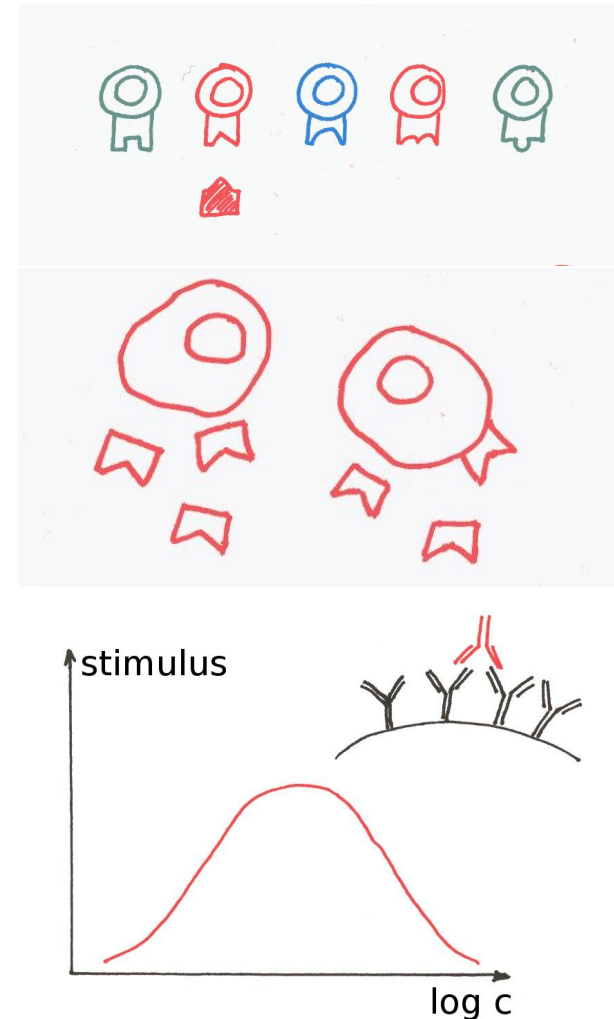
The B-lymphocyte System

- B-lymphocytes carry receptors (antibodies) of a certain specificity (idiotype).
- The specificity is determined by the protein surface of the variable region of the antibody.
- Antibodies bind complementary structures (antigens or antibodies).



Clonal Selection

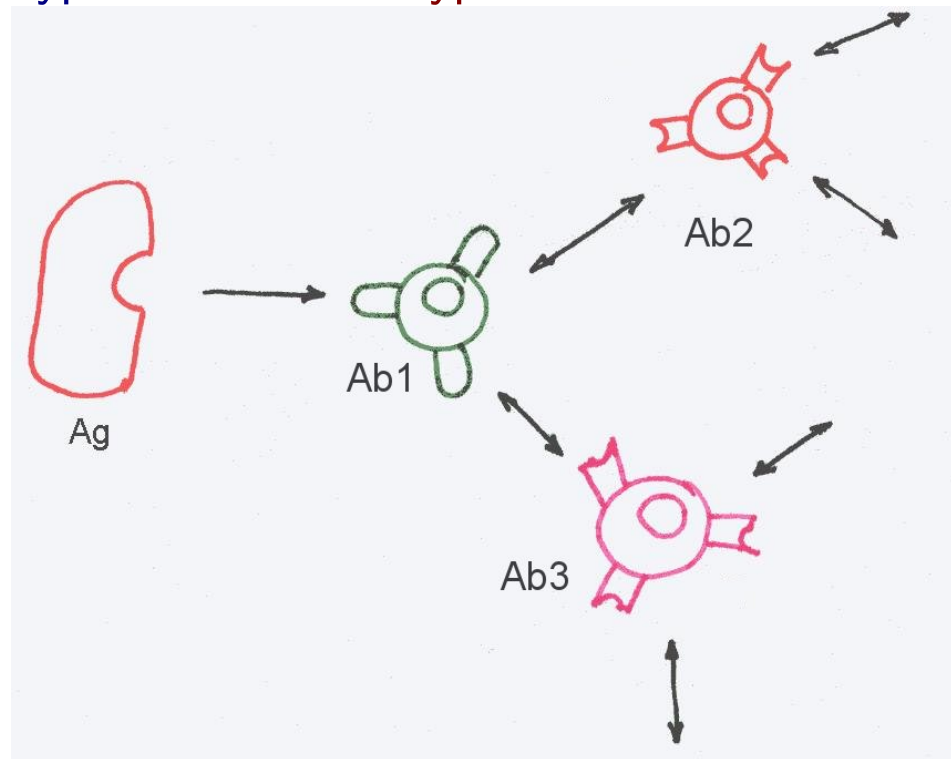
- B-lymphocytes of random specificity are produced continuously in the **bone marrow**.
- If the receptors are crosslinked by *complementary* structures (**antigens** or **antibodies**), B-lymphocytes proliferate and produce large amounts of antibodies. Unstimulated B-cell clones die out. (**Clonal selection**⁴)
- The response curve is log-bell shaped.



⁴F.M. Burnett, The Clonal Selection Theory of Acquired Immunity, Vanderbilt Univ. Press, Nashville, TN (1959)

Idiotypic Networks

- Complementary idiotypes form an **Idiotypic network**.⁵



- There is a dynamics independent from antigens.
- Immunologic memory by internal images of antigen.
- Repertoire of idiotypes: potential 10^{12} , expressed 10^7
- Network architecture: **Central** (highly connected) and **peripheral** (isolated) part.⁶

⁵N.K. Jerne, Towards a network theory of the immune system, Ann. Inst. Pasteur Immunol. **125C**, 373 (1974)

⁶A. Coutinho, Beyond clonal selection and network, Immunol. Rev. **110**, 63 (1989)

The Bitstring Model

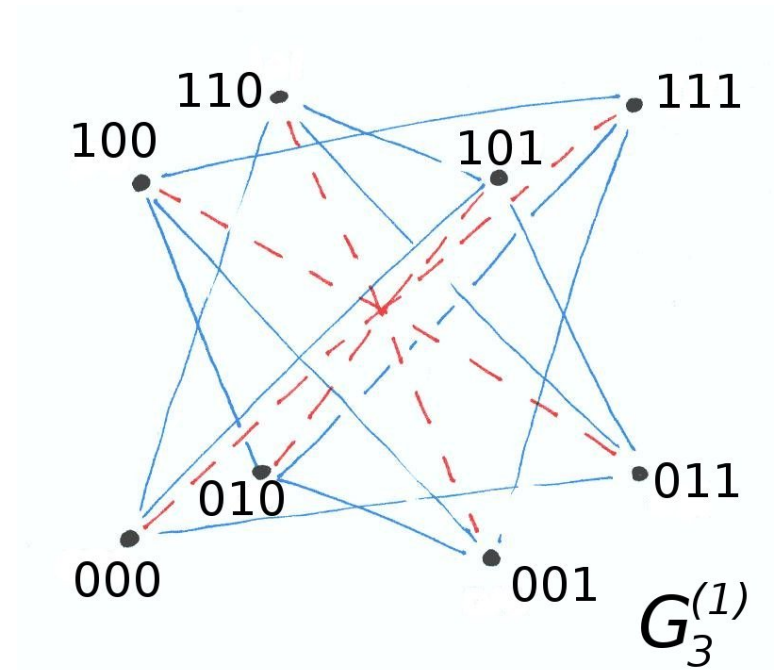
Base graph:

- Idiotypes shapes (vertices) are characterized by **bitstrings** of length d .
- Interaction (links) between complementary and almost complementary idiotypes (allow m **mismatches**).

Idiotype 011101001100

Complementary Idiotype 10001**1**110011

- Vertices can be occupied or unoccupied.

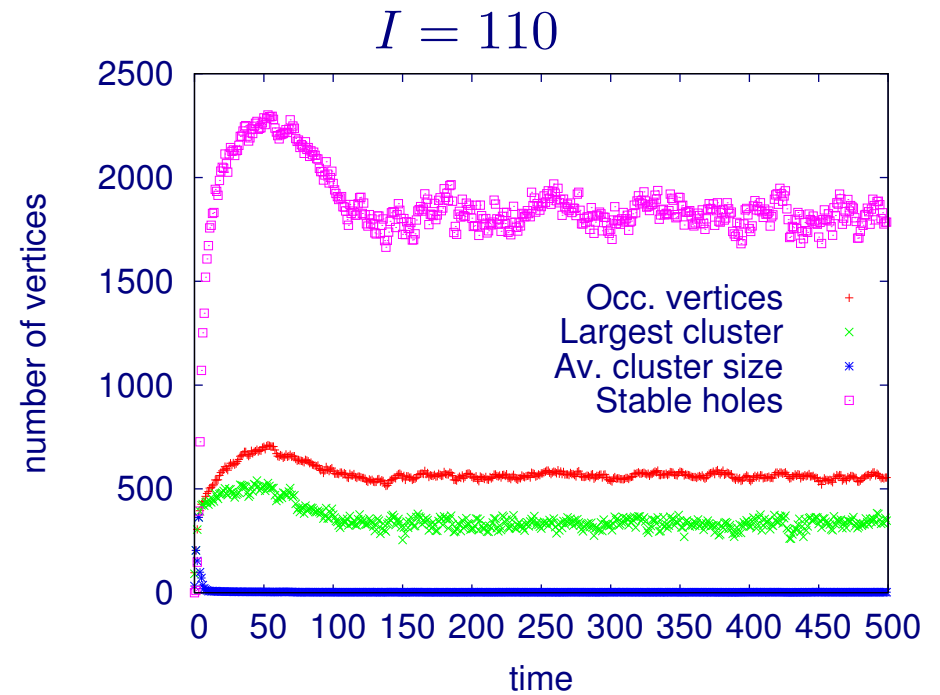
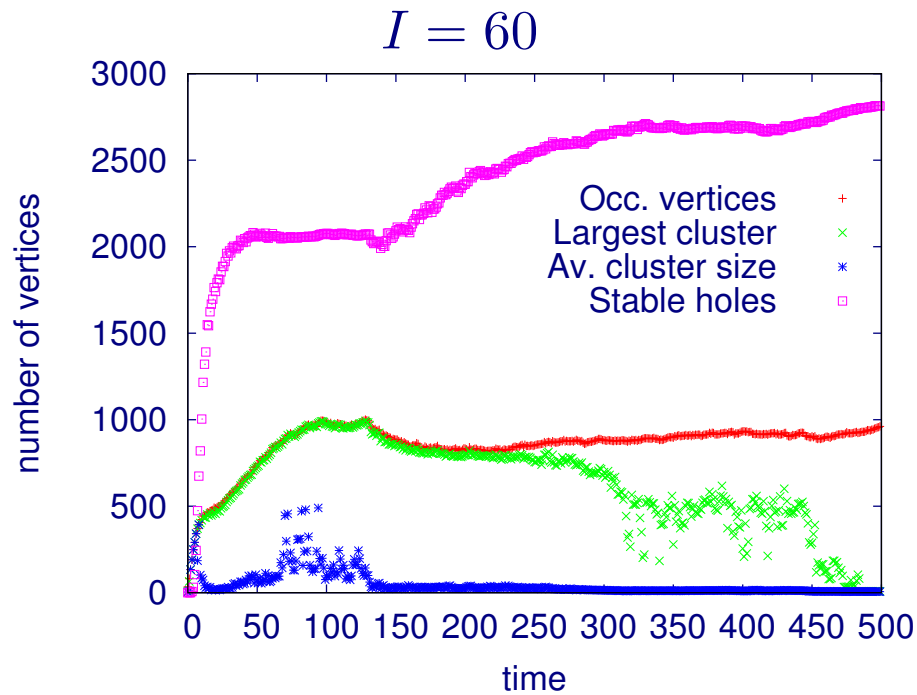


Update algorithm:

- Random influx:** Choose I unoccupied sites (holes) randomly and set them occupied.
- Population dynamics:** Clear an occupied vertex if its number of occupied neighbors is outside a window (t_l, t_u) .
- Iteration:** Repeat steps (i) and (ii).

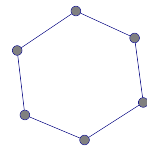
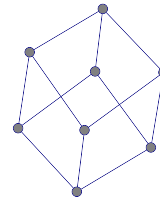
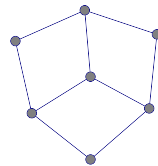
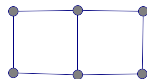
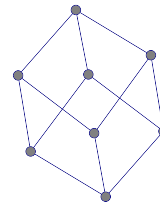
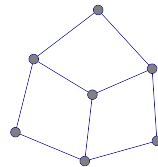
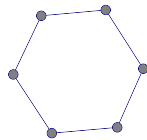
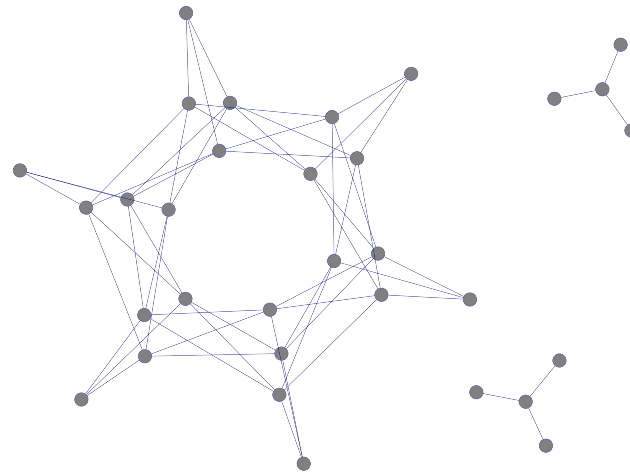
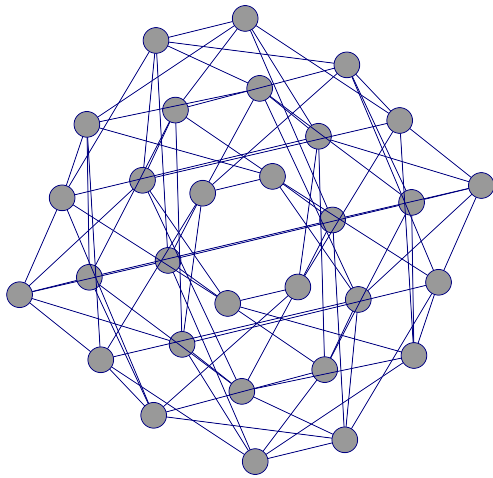
Simulation Results

Time series of a simulation on $G_{12}^{(2)}$ with $(t_l, t_u) = (1, 10)$:

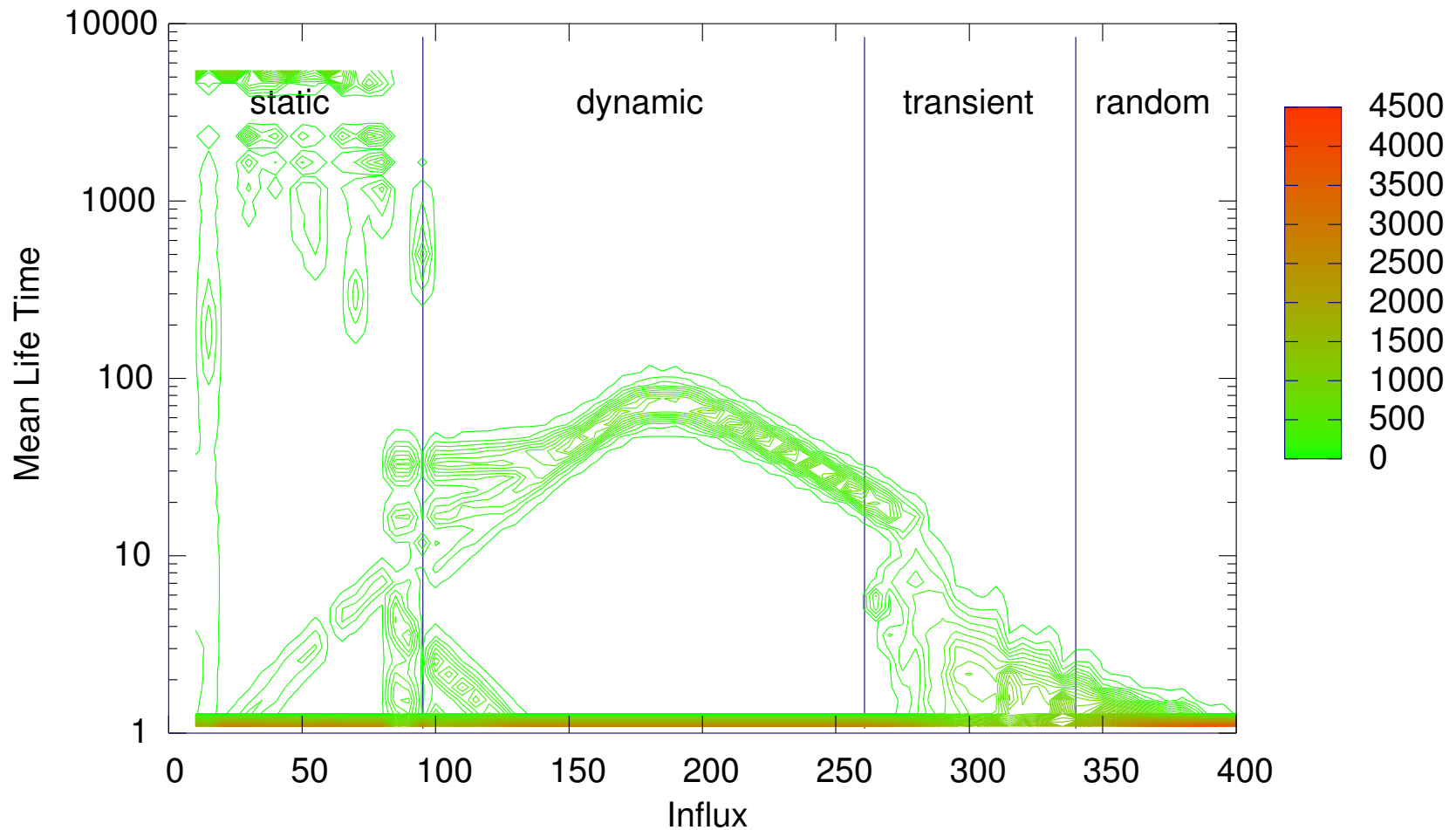


The model idiosyncratic network evolves randomly and reaches a **stationary state** with a characteristic pattern.

Example Patterns

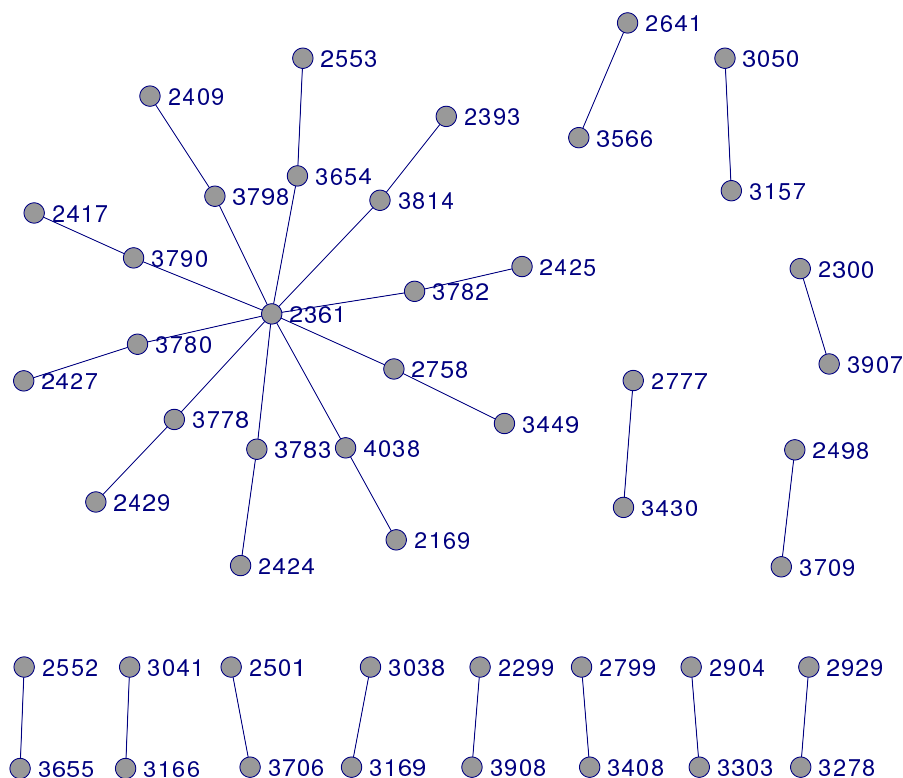


Simulation Results



Parameters: base graph $G_{12}^{(2)}$, $(t_l, t_u) = (1, 10)$, $(T_0, T_1) = (5000, 10000)$

2-cluster Pattern



Simulation on
base graph $G_{12}^{(2)}$
 $(t_l, t_u) = (1, 10)$
 $I = 10$

Index sum in 2-clusters
is constant:

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

	occ. vertices (S_1)	pot. hubs (S_2)	stable 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

Only 2 bits determine the behavior of a vertex.

We say the 2-cluster pattern on $G_d^{(2)}$ has 2 **determinant bits**:

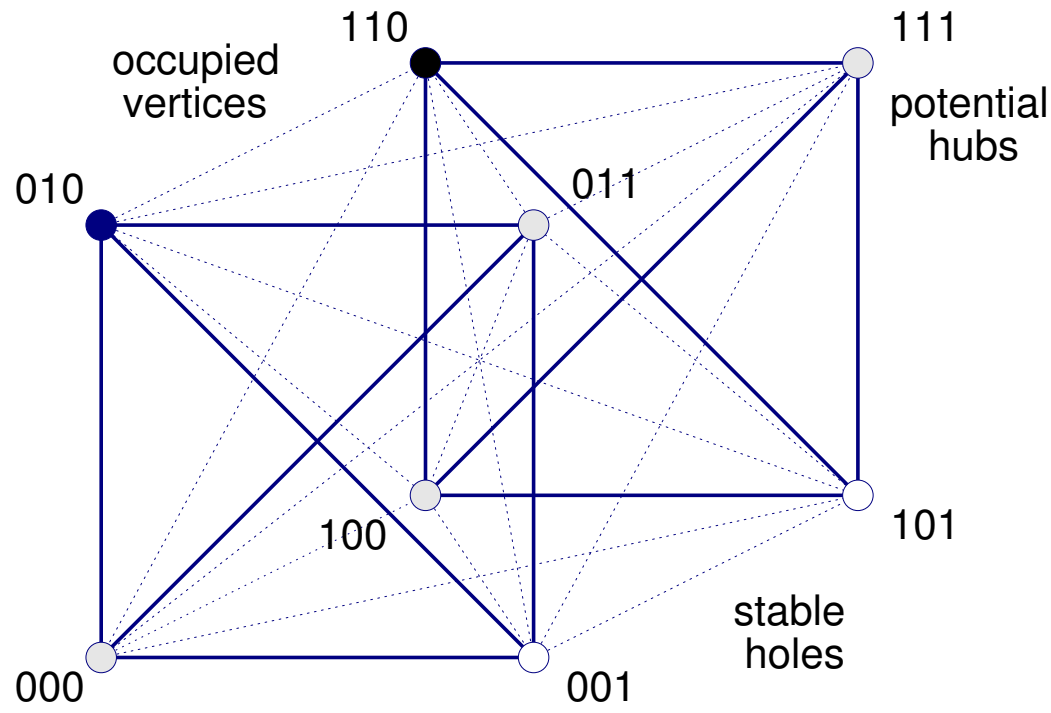
occupied vertices S_1	$\dots b_k \dots b_l \dots$
potential hubs S_2	$\dots \overline{b_k} \dots \overline{b_l} \dots$
stable holes S_3	$\dots b_k \dots \overline{b_l} \dots$

Applying these principles we can *calculate* $n(\partial v)$ by simple combinatorics:

$$n(\partial v) = \sum_{j=0}^{i-1} \binom{d-2}{j} \text{ with } v \in S_i$$

	S_1	S_2	S_3
$n(\partial v)_{\text{combin}}$	1	11	56
$n(\partial v)_{\text{sim}}$	1.16	10.96	53.26

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



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

A **pattern module** comprises vertices with identical non-determinant bits.

The **determinant bits** are the coordinates of corners of a 2-dimensional **hypercube**.

Congruently occupied, $(2^{d-2}$ -fold) **repeating** pattern modules are the building blocks of the pattern.

Generalizations

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

For a given base graph $G_d^{(m)}$ and a pattern module dimension d_M we can calculate the number of groups $d_M + 1$, their relative sizes $|S_i| = 2^{d-d_M} \binom{d_M}{i-1}$, and their interconnectivity.

d_M	relative size of different groups							observed patterns in $G_{12}^{(2)}$
0	1							
1	1		1					
2	1		2		1		2-cluster pattern	
3	1		3		3		1	
4	1		4		6		4	
5	1		5		10		10	
6	1		6		15		20	
...	...		...		...		...	

Linking between groups

The possible links between vertices of different groups are constrained by the **mismatch rule** and –in particular– by mismatches in the **determinant bits**.

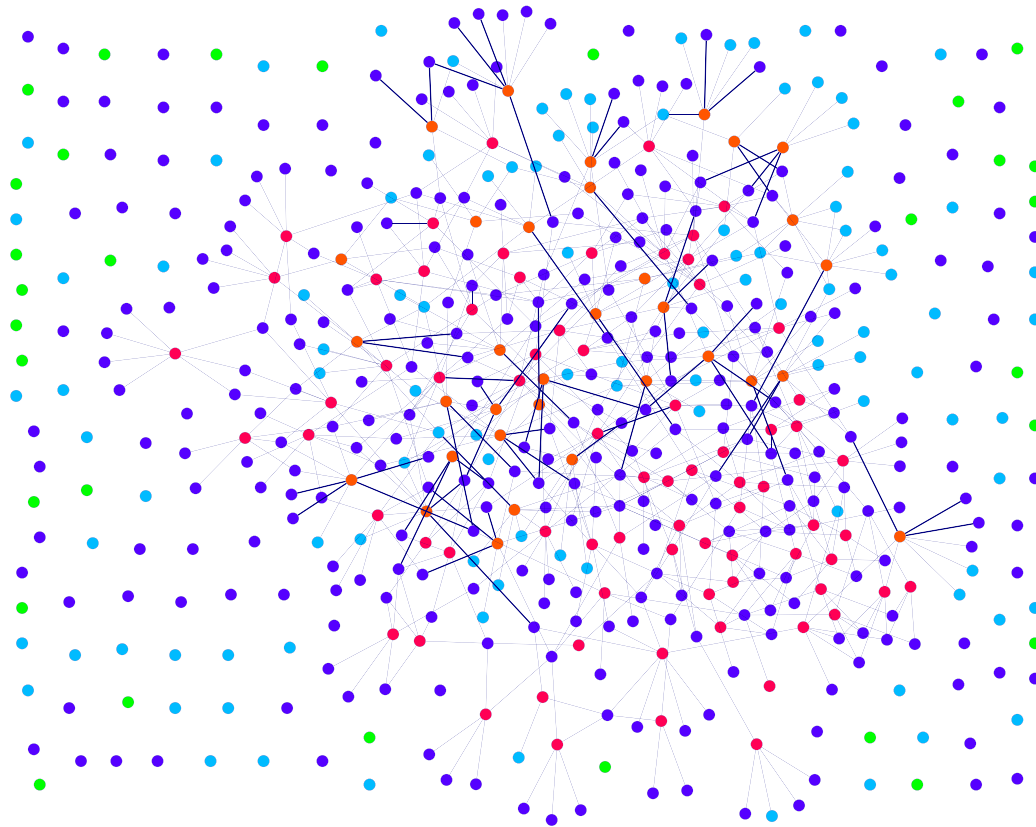
$$\begin{array}{rcl}
 v_i : & \bar{b}_{k_1} & \bar{b}_{k_2} \quad \dots \quad \bar{b}_{k_{i-1}} \quad b_{k_i} \quad \dots \quad \dots \quad \dots \quad \dots \quad b_{k_{d_M}} \\
 v_j : & b_{k_1} & b_{k_2} \quad \dots \quad \dots \quad \dots \quad \dots \quad b_{k_{d_M-j+1}} \quad \bar{b}_{k_{d_M-j+2}} \quad \dots \quad \bar{b}_{k_{d_M}} \\
 & \underbrace{\hspace{10em}}_{i-1 \text{ bits}} & \underbrace{\hspace{10em}}_{m_{ij}^{\min} := d_M - i - j + 2 \text{ bits}} & \underbrace{\hspace{10em}}_{j-1 \text{ bits}}
 \end{array}$$

Elementary combinatorics give the number of links of a vertex $v_i \in S_i$ to vertices of S_j :

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

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

The Dynamic Six-group Pattern on $G_{12}^{(2)}$



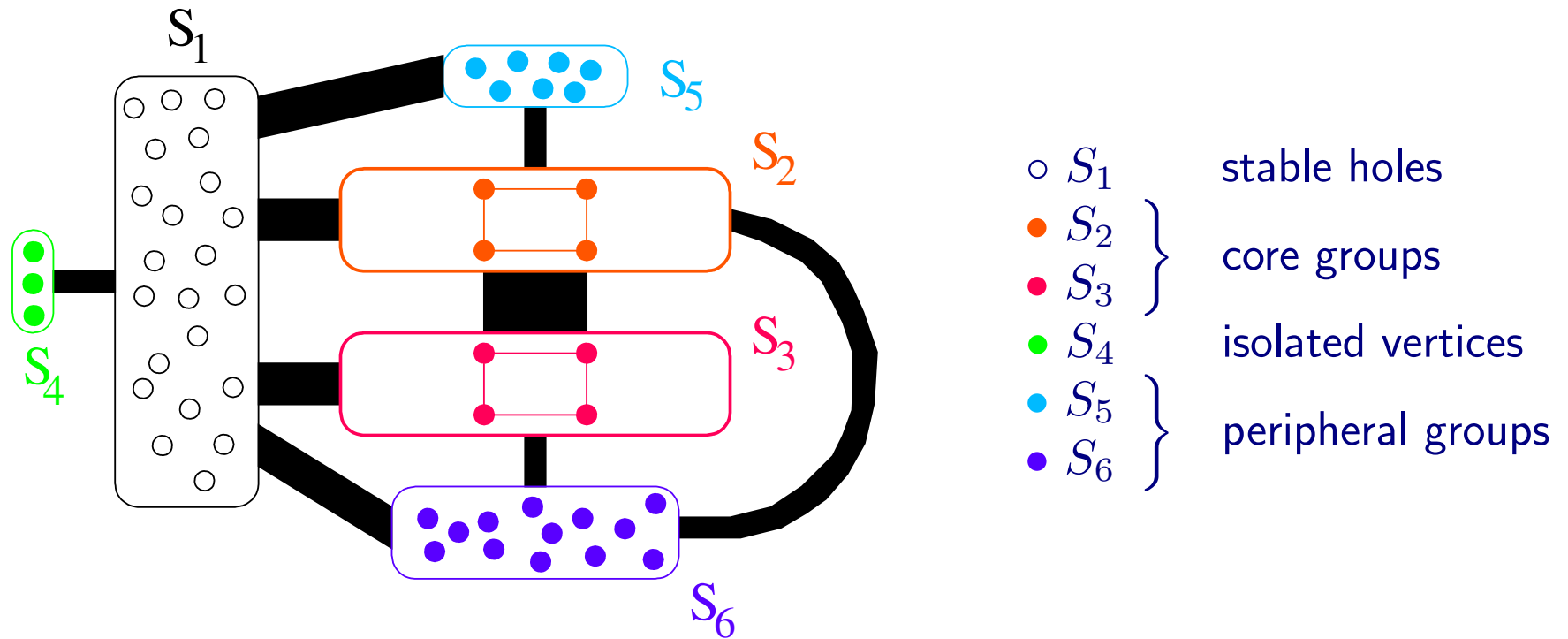
- S_1 stable holes
- S_2 } core groups
- S_3 }
- S_4 isolated vertices
- S_5 } peripheral groups
- S_6 }

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

$$I = 90$$

		S_1	S_2	S_3	S_4	S_5	S_6
Group size	$ S_i $	1124	924	924	134	330	660
Mean life time	$\langle \tau(v) \rangle_{S_i}$	0.0	3.8	5.4	10.0	18.1	35.6
Mean occupation	$\langle n(v) \rangle_{S_i}$	0.0	0.029	0.066	0.198	0.324	0.482

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 Dynamic Six-group Pattern

The six-group pattern can be explained considering an 11-dimensional pattern module.

The **group size**:

	S'_1	S'_2	S'_3	S'_4	S'_5	S'_6	S'_7	S'_8	S'_9	S'_{10}	S'_{11}	S'_{12}
empirical group	S_4	S_4	S_4	S_5	S_6	S_3	S_2	S_1	S_1	S_1	S_1	S_1
group size	2	22	110	330	660	924	924	660	330	110	22	2

The **number of links** of a vertex $v_i \in S_i$ to vertices of S_j :

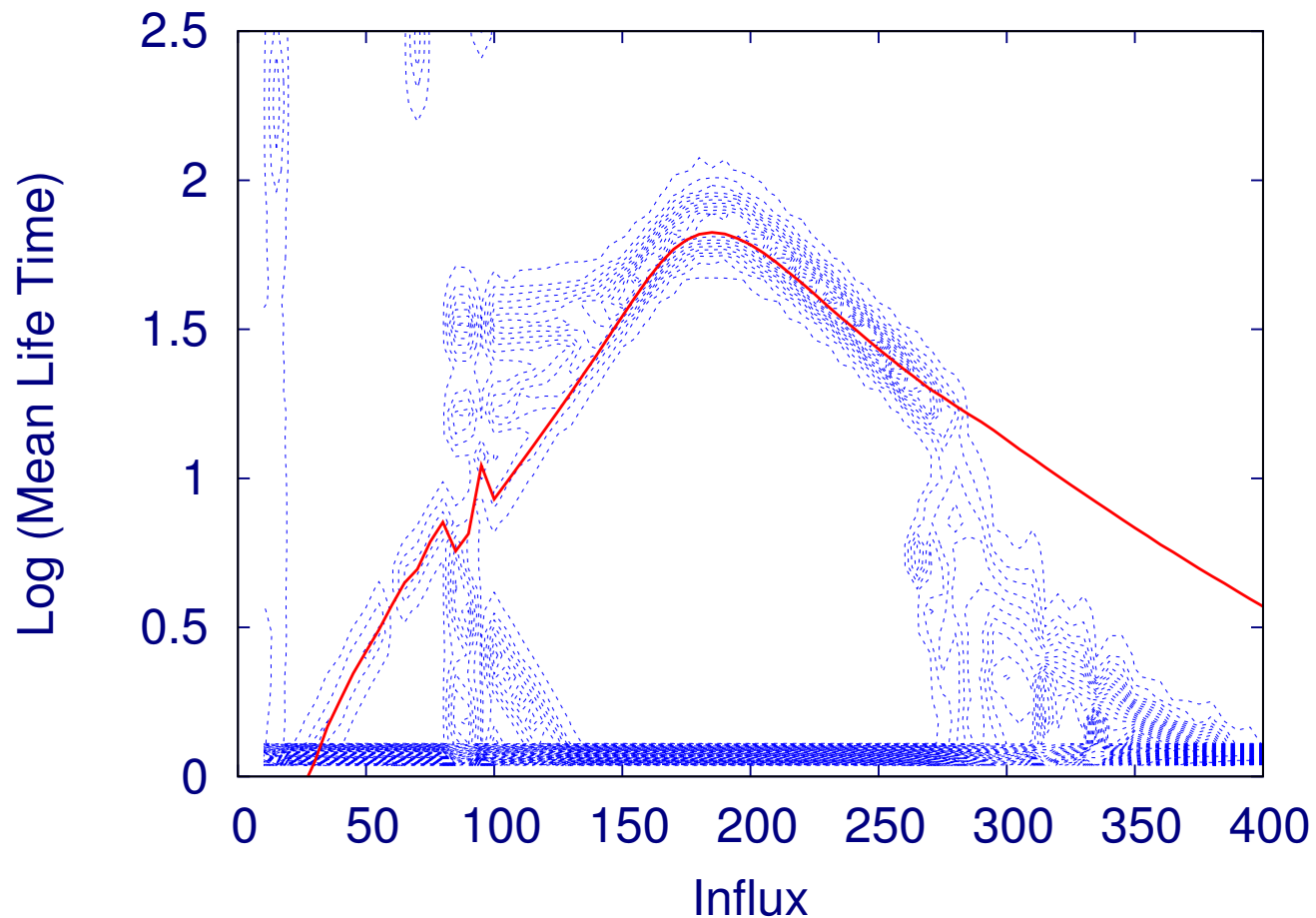
	S_1	S_2	S_3	S_4	S_5	S_6
v_1	0	12,3	16,4	9,4	15	25,8
v_2	15	12	32	0	10	10
v_3	20	32	12	0	0	15
v_4	79	0	0	0	0	0
v_5	51	28	0	0	0	0
v_6	44	14	21	0	0	0

The combinatorial results are **identical** with the simulation results!

Mean Field Theory

Mean life time of a node surrounded by stable holes:

$$\langle \tau \rangle = \frac{P_0}{1 - P_0}, \quad P_0 = \sum_{k=t_l}^{t_u} \binom{\kappa}{k} p^k (1 - p)^{\kappa - k}$$



Summary

Structural understanding of the architecture of a randomly evolving network

Architecture with many features of the biological network

Analytical results in excellent agreement with simulations

Outlook

Mean field theory: mean occupation, mean lifetime depending on influx

Stability of patterns, transitions, ergodicity breaking

Scaling to realistic network sizes applying renormalization group

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

Co-evolution with a growing antigen