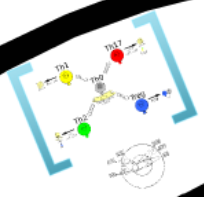
Linfocitos T cooperadores

regulan la respuesta inmune adaptativa



¿Como está regulada la diferenciación de las células Th?

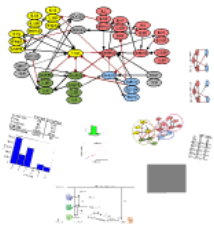
Modelación

Redes

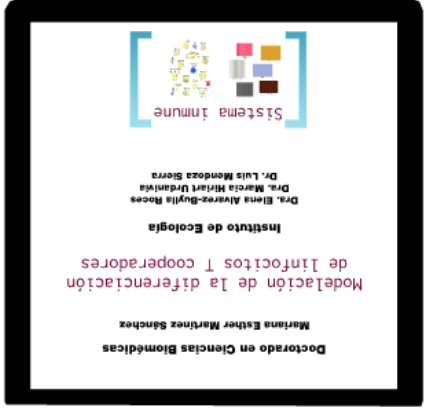
Reglas

Cadenas de Markov

Poblacional



Problemas



Bibliográfia

Doctorado en Ciencias Biomédicas

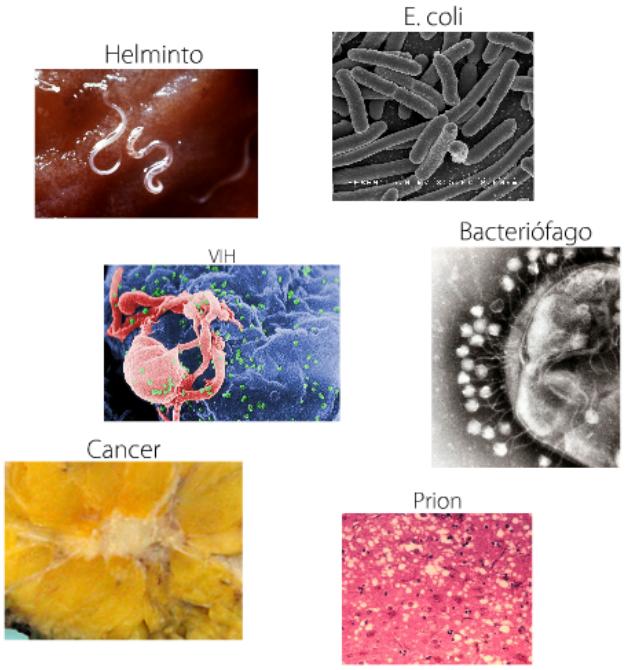
Mariana Esther Martínez Sánchez

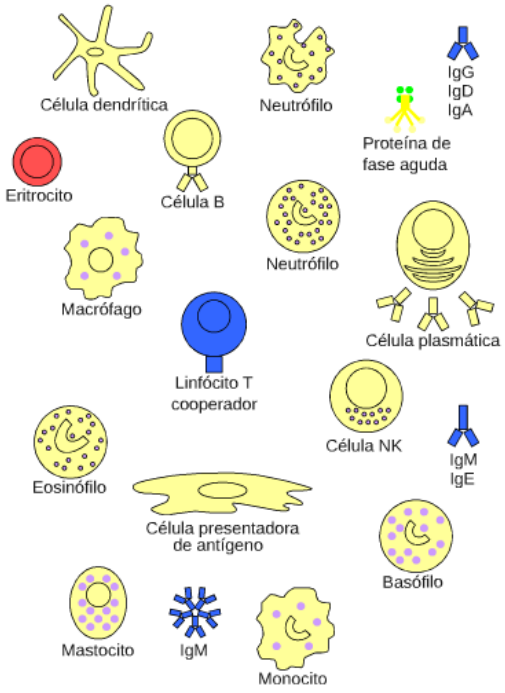
Modelación de la diferenciación de linfocitos T cooperadores

Instituto de Ecología

Dra. Elena Alvarez-Buylla Roces
Dra. Marcia Hiriart Urdanivia
Dr. Luis Mendoza Sierra

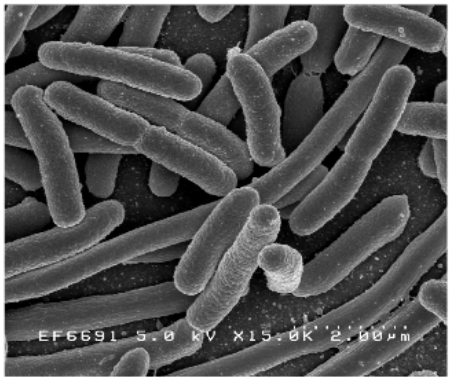
Sistema inmune



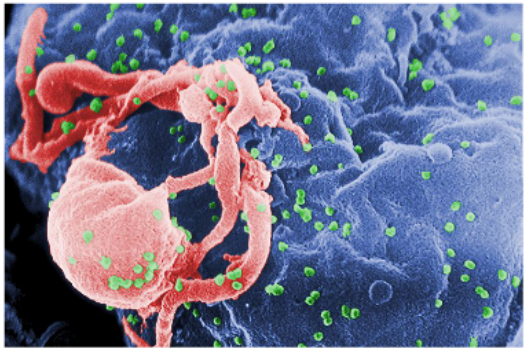


Helminto

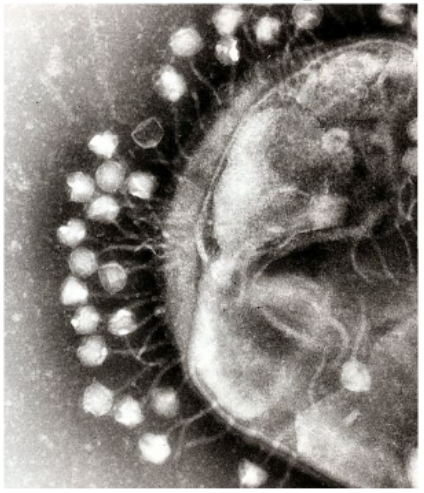
E. coli



VIH

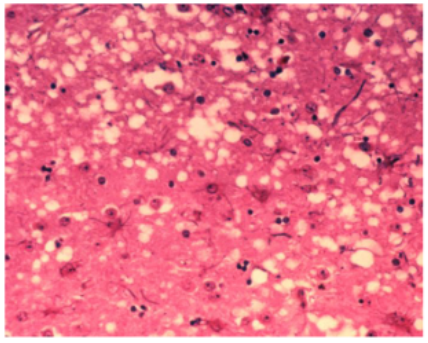


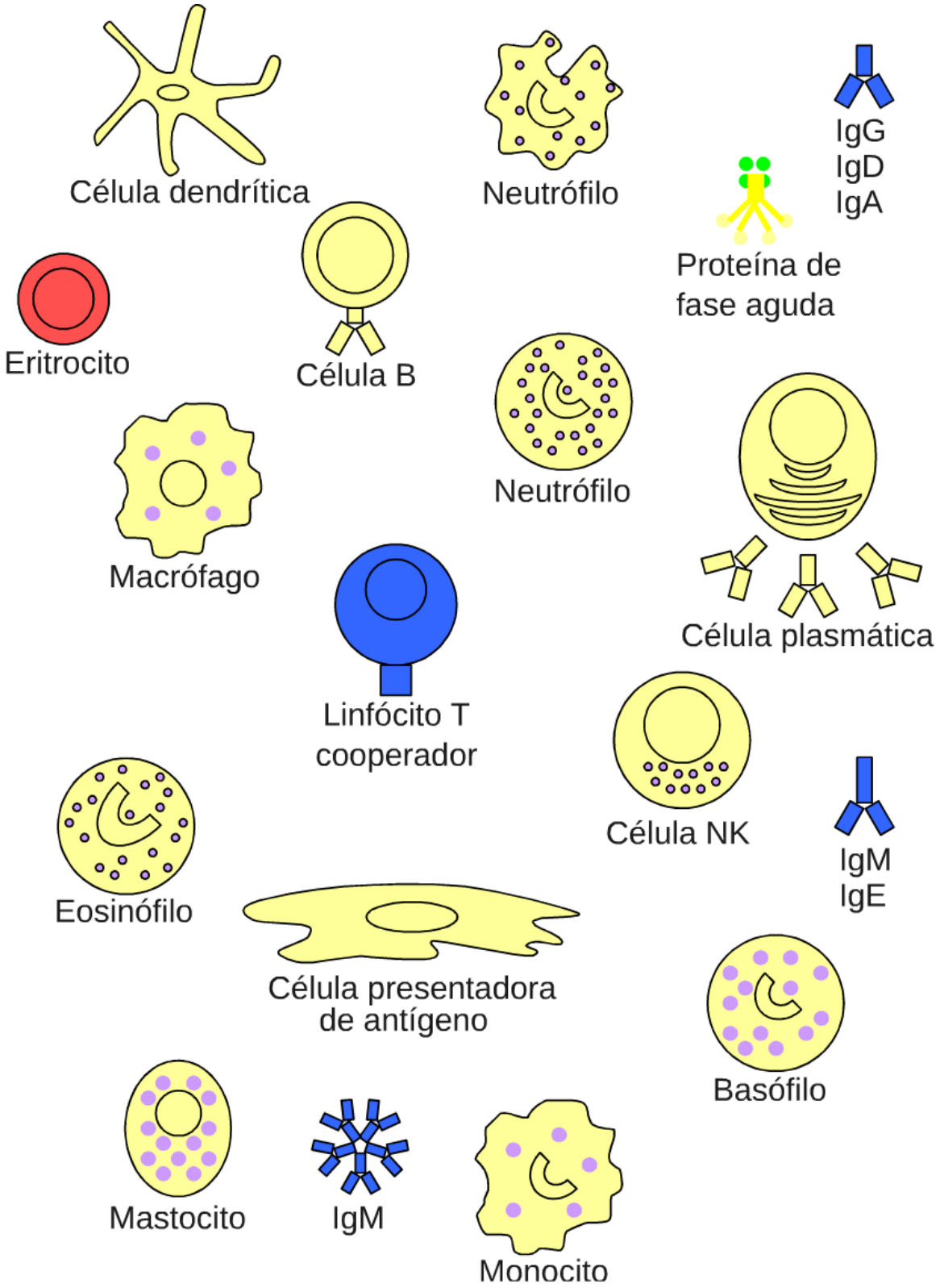
Bacteriófago



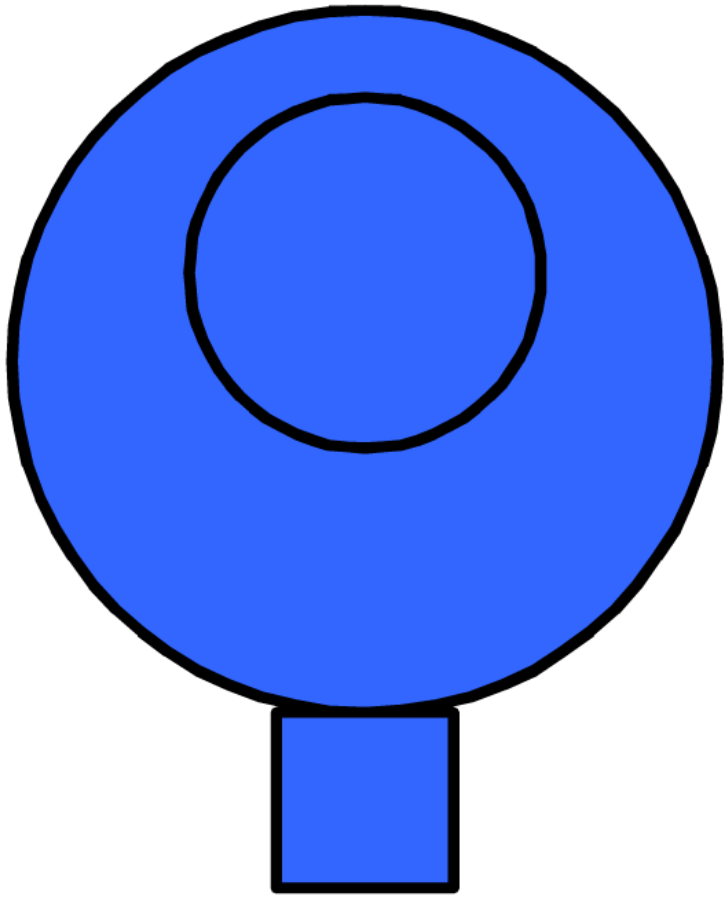
Cancer

Prion




Célula dendrítica
Neutrófilo
IgG
IgD
IgA
Proteína de
fase aguda
Eritrocito
Célula B
Neutrófilo
Macrófago
Célula plasmática
Linfócito T
cooperador
Célula NK
IgM
IgE
Eosinófilo
Célula presentadora
de antígeno
Basófilo
Mastocito
IgM
Monocito

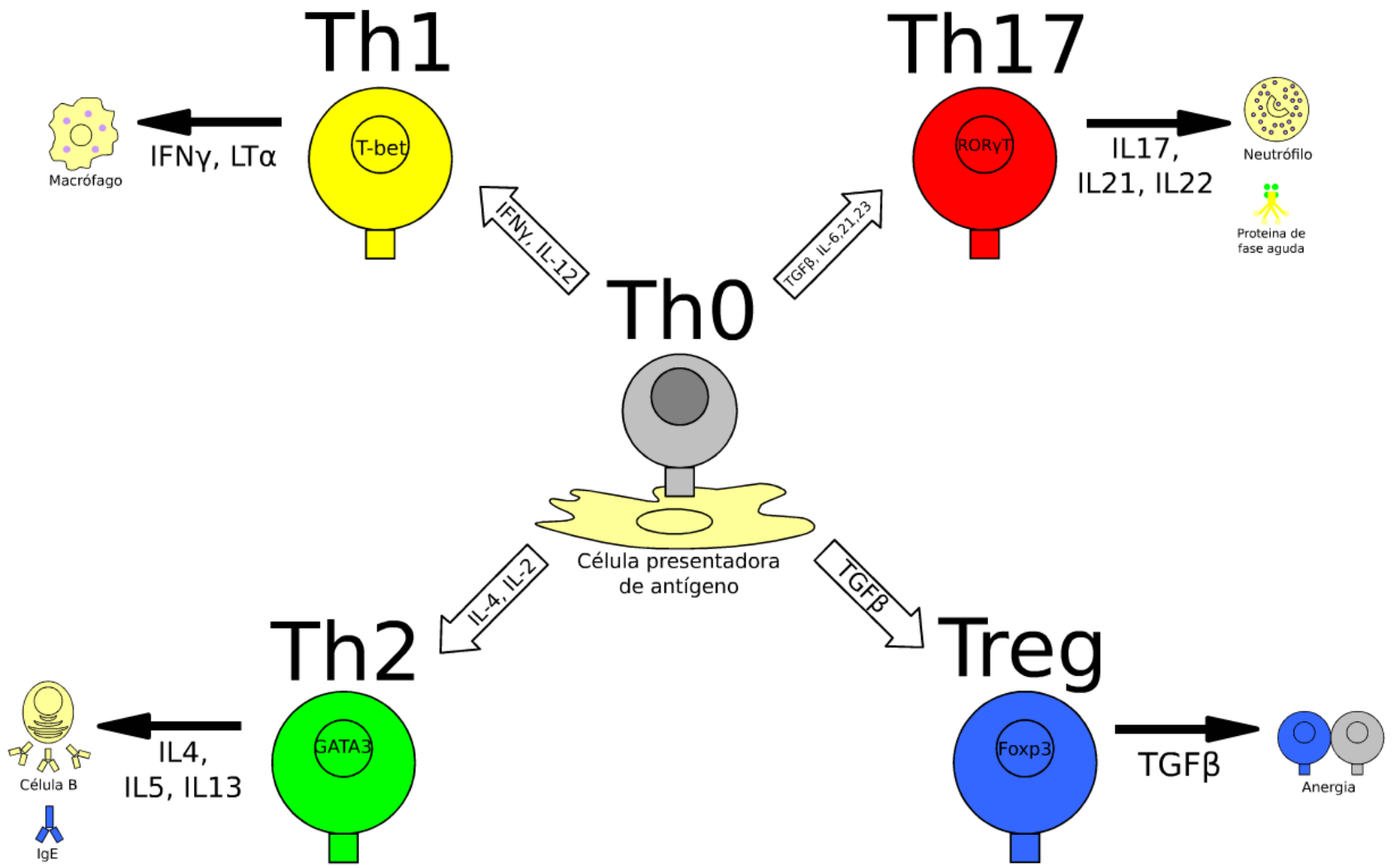
ago

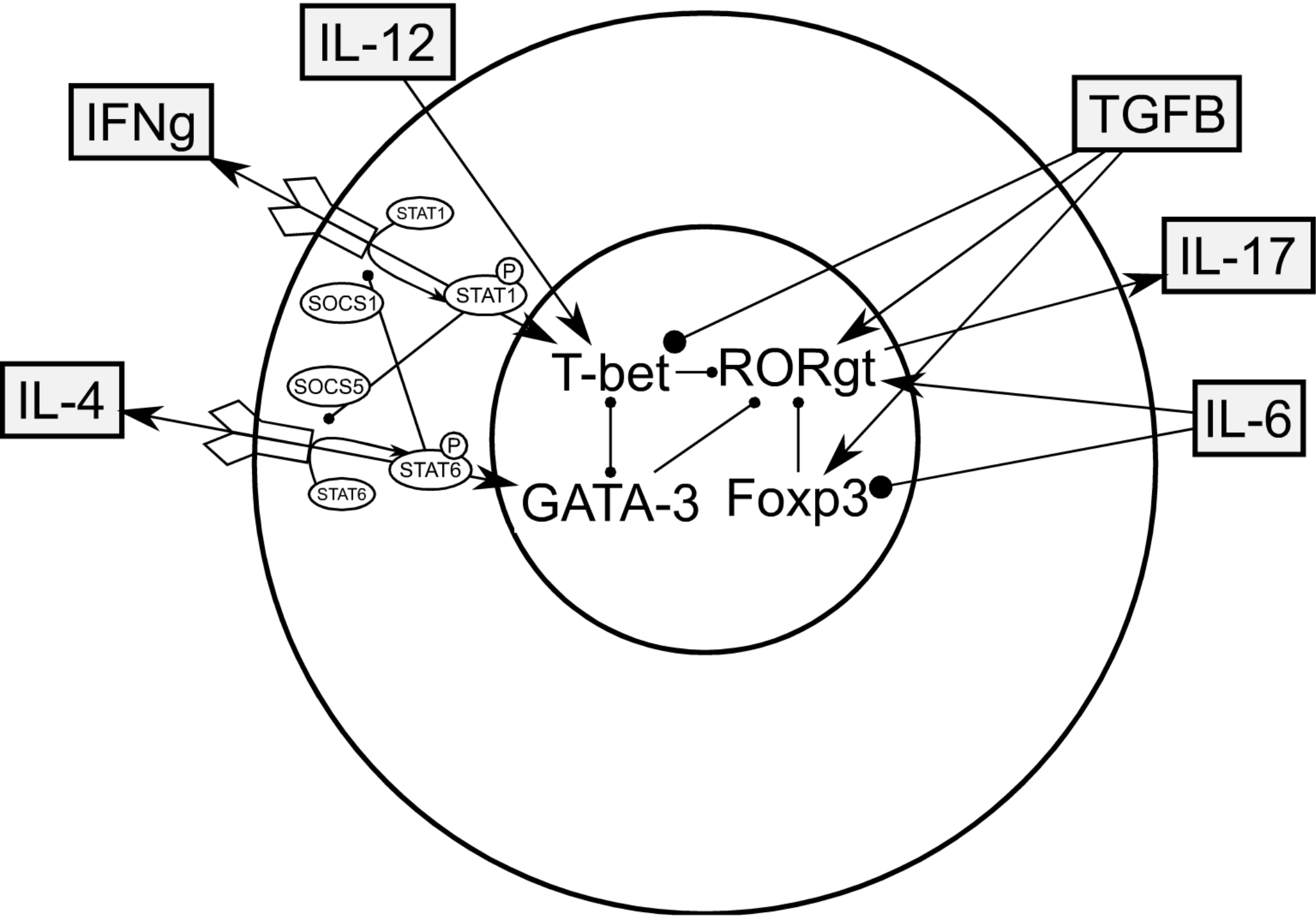


Linfócito T cooperador

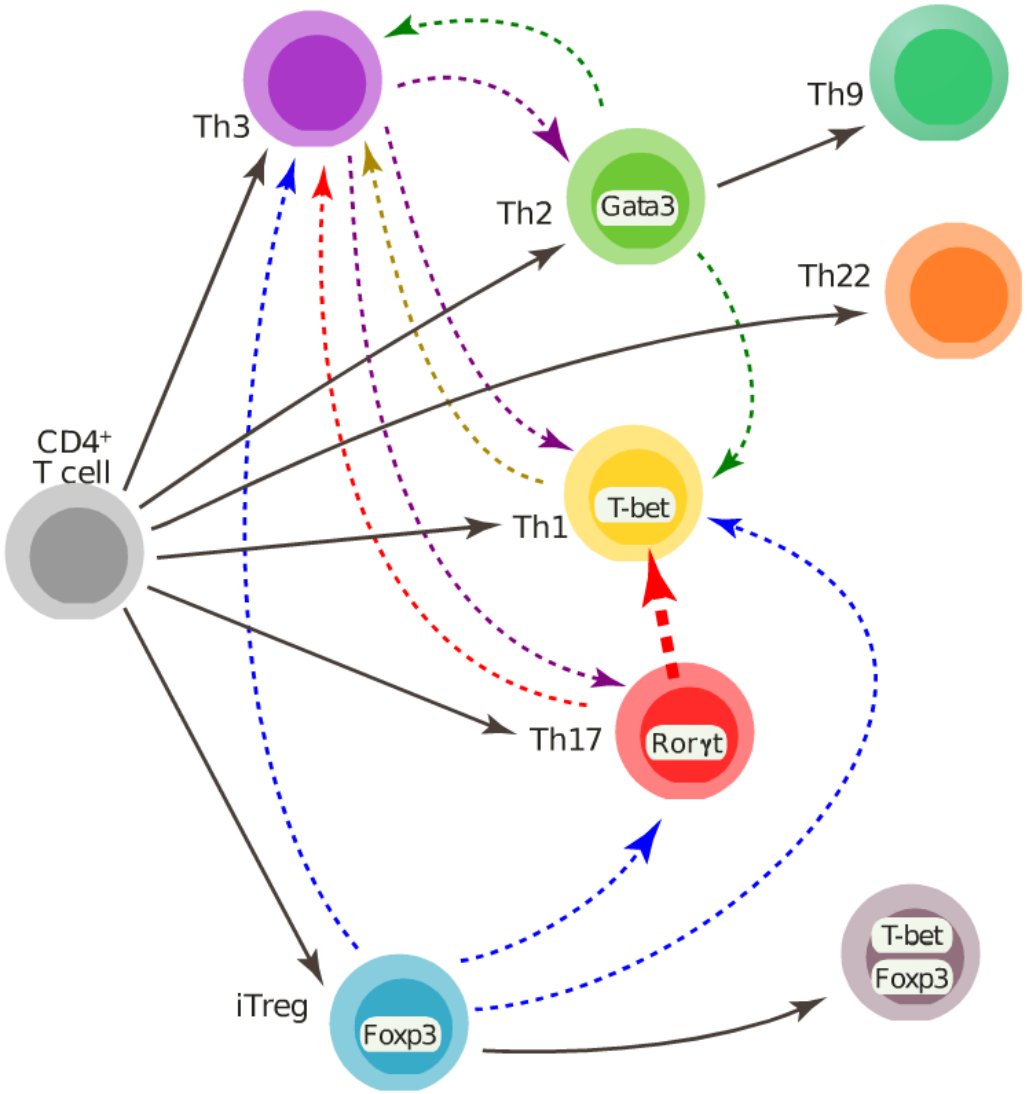
Linfocitos T cooperadores

regulan la respuesta inmune adaptativa


Th1
T-bet
IFNγ, LTα
Macrófago
Th17
RORγT
IL17,
IL21, IL22
Neutrófilo
Proteina de
fase aguda
IFNγ, IL-12
TGFβ, IL-6,21,23
Th0
Célula presentadora
de antígeno
IL-4, IL-2
TGFβ
Th2
GATA3
IL4,
IL5, IL13
Célula B
IgE
Treg
Foxp3
TGFβ
Anergia

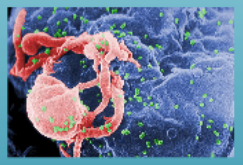

IL-12
IFNg
TGFB
IL-17
IL-4
IL-6
STAT1
P
STAT1
SOCS1
SOCS5
T-bet
RORgt
P
STAT6
STAT6
GATA-3
Foxp3

plasticidad



Importancia

VIH



Th1
Th0
Th2

Clericia 93, Maggi 94

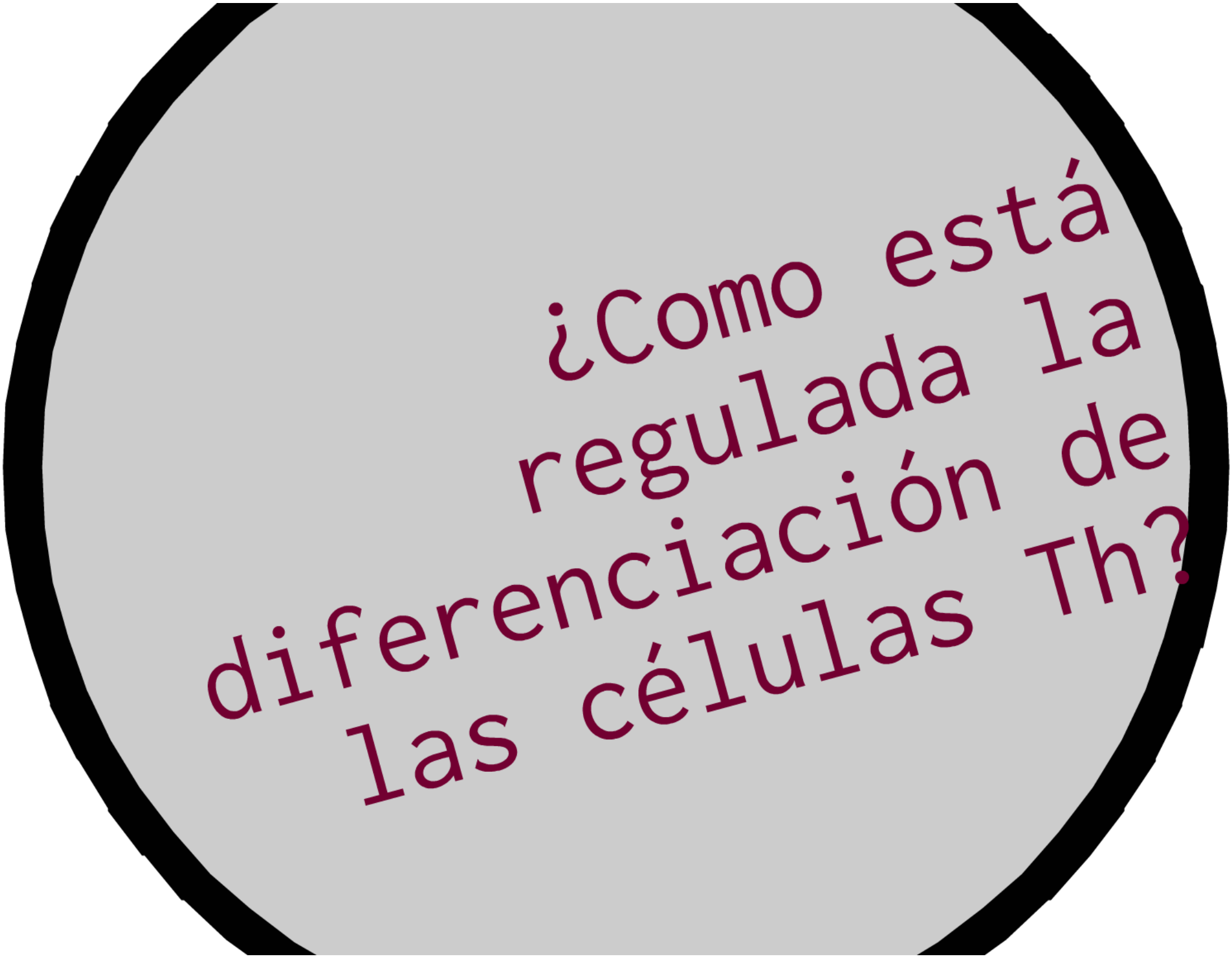
enfermedades autoinmunes

asma
cancer
encefalomielitis
esclerosis múltiple
artritis reumatoide
inflamaciones gástricas
CVID (Common Variable Immunodeficiency)

diabetes

inflamación
Th1
Treg

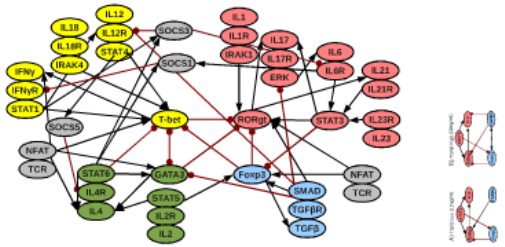
Winer 09, Feuerer 09


¿Como está regulada la diferenciación de las células Th?

las celu

Modelación

Redes

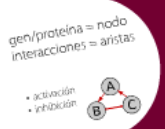


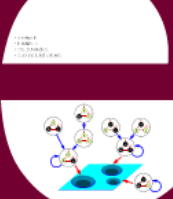
Reglas

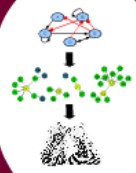
Cadenas
de Markov

Poblacional

Redes







revisiones

Estocásticas

elementos aleatorios

activación genes

proteínas

tiempo

Booleanas

Dinámicas
Discretas
- prendido (1)
- apagado (0)

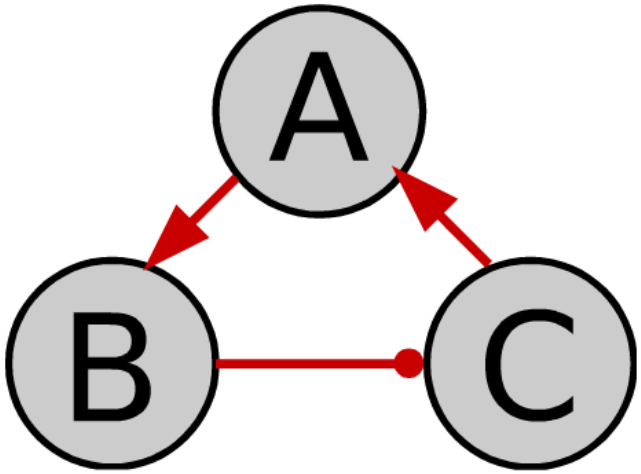
Continuas

Proteinas
- Síntesis
- Degradación
- Señalización

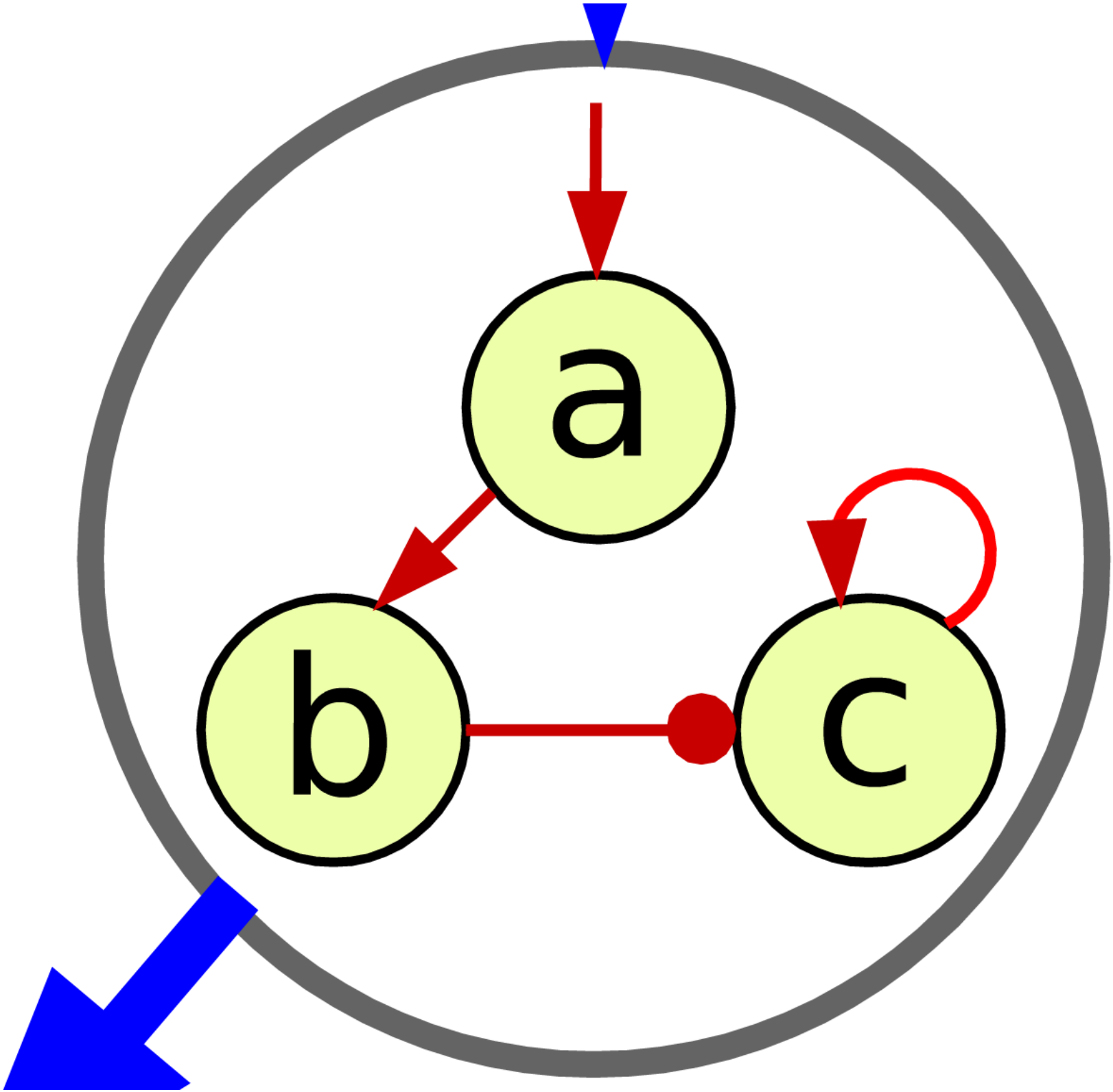
gen/proteína = nodo

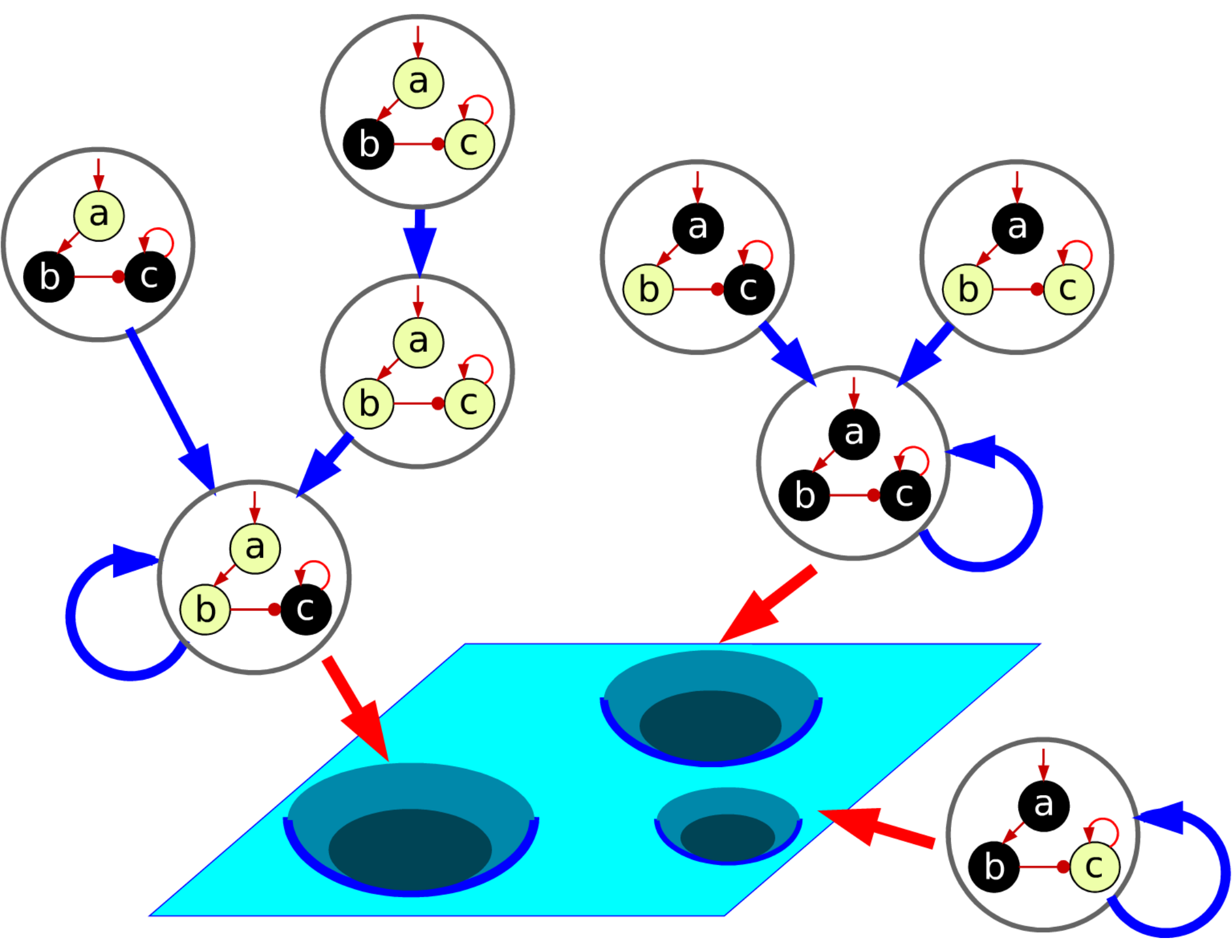
interacciones = aristas

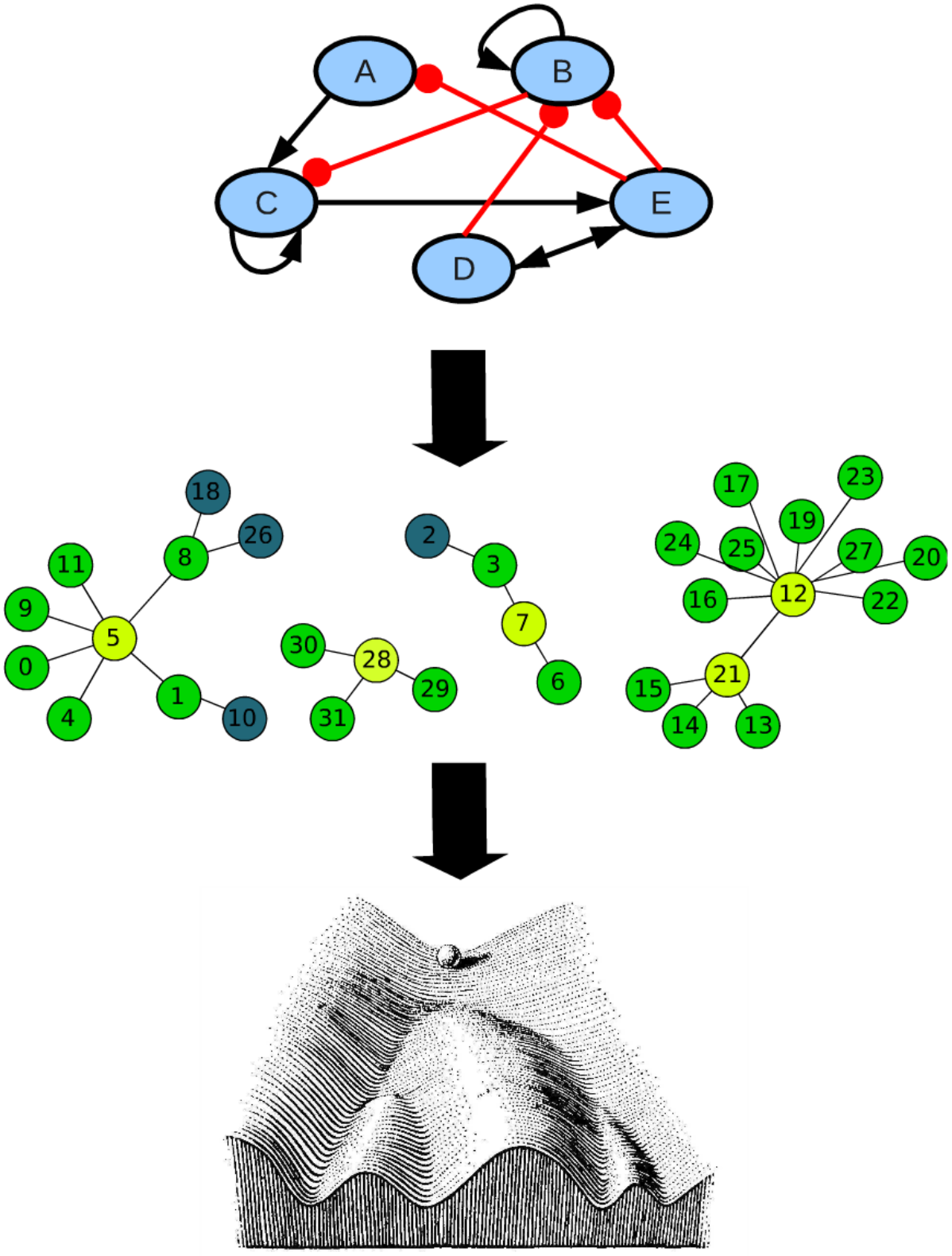
- activación
- inhibición



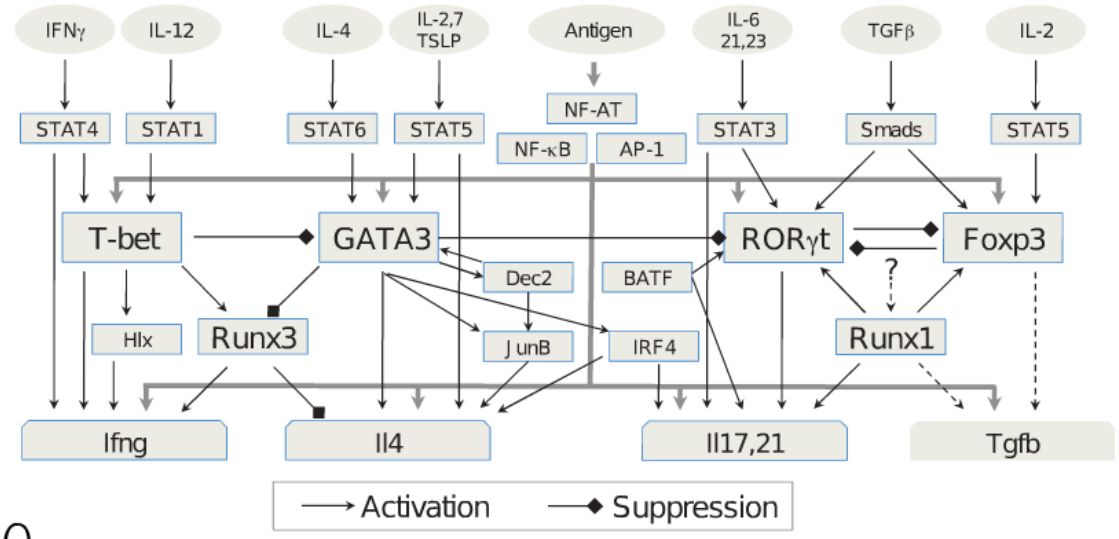
- a activa b
- b inhibe c
- c se autoinduce
- a es una señal externa


a
b
c


a
b
c


A
B
C
D
E
18
26
8
11
9
5
0
4
1
10
30
28
29
31
2
3
7
6
17
23
19
24
25
27
20
16
12
22
21
15
14
13

revisiones



Murphy 10

Zhu 10

Booleanas

Dinámicas

Discretas

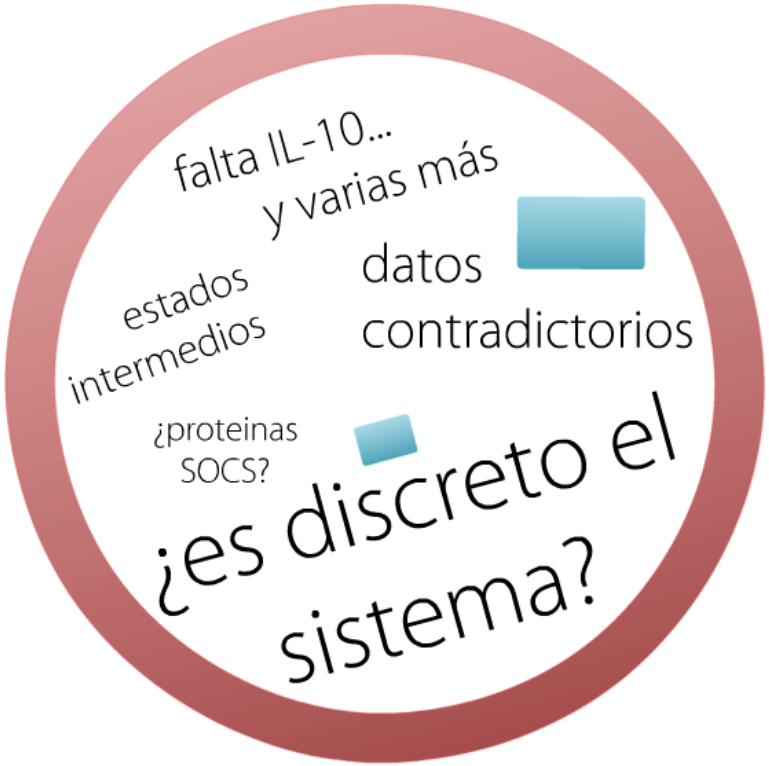
- prendido (1)
- apagado (0)

Dirigidas

Finitas

Deterministas

Fácil análisis



Continuas

Proteinas

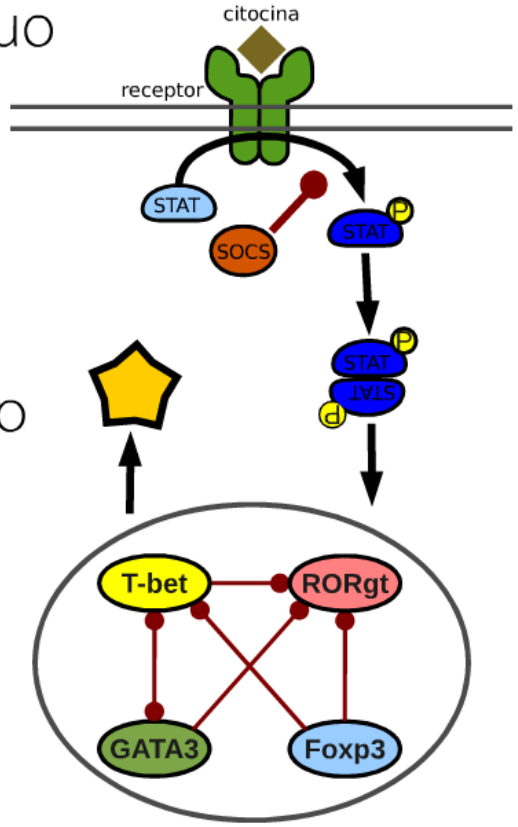
- Síntesis
- Degradación
- Señalización

Faltan parámetros cuantitativos

Dinámicas
Dirigidas
Deterministas
Continuas (sigmoidal)

Híbridas

continuo



discreto

buscando parámetros

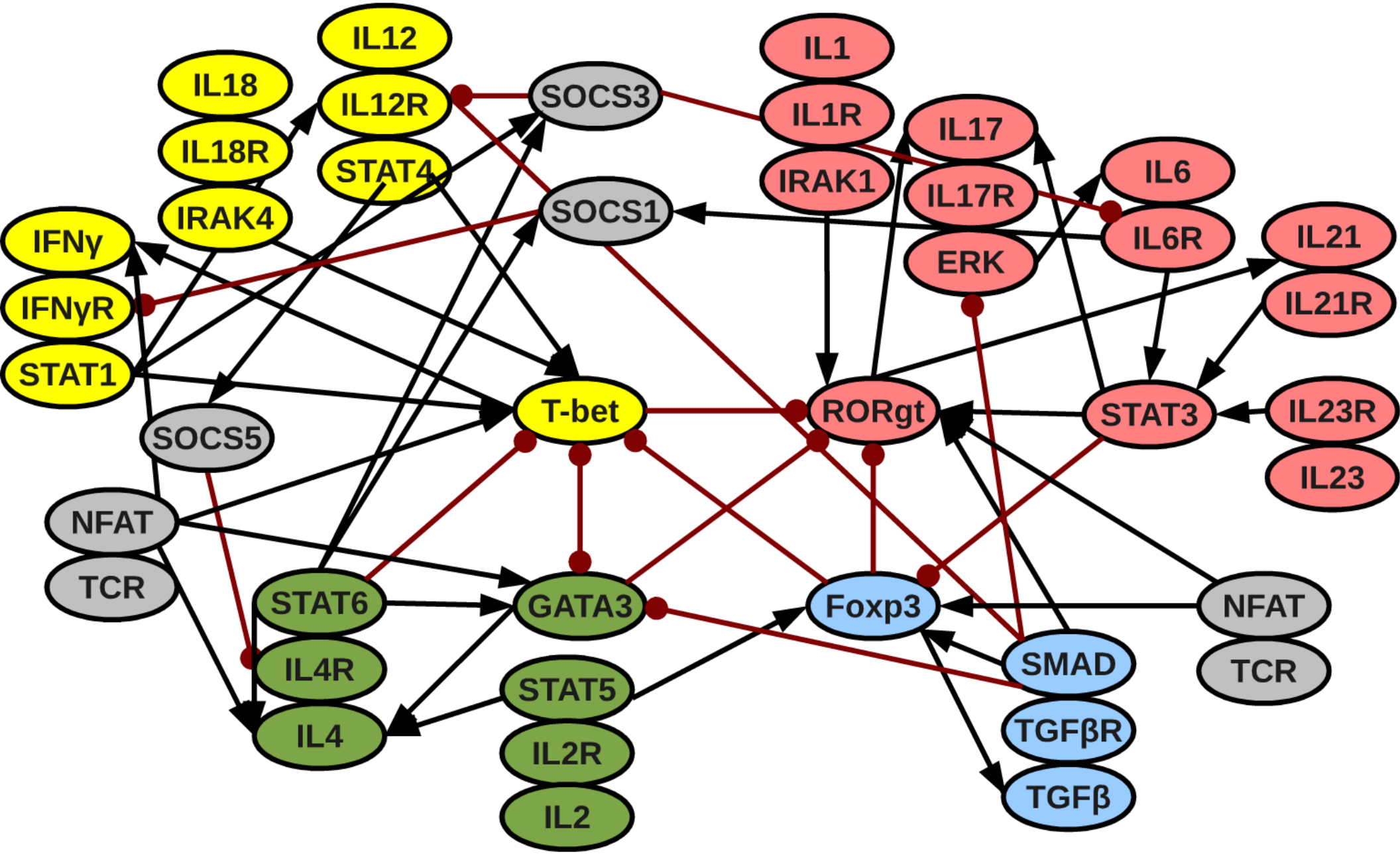
Estocásticas

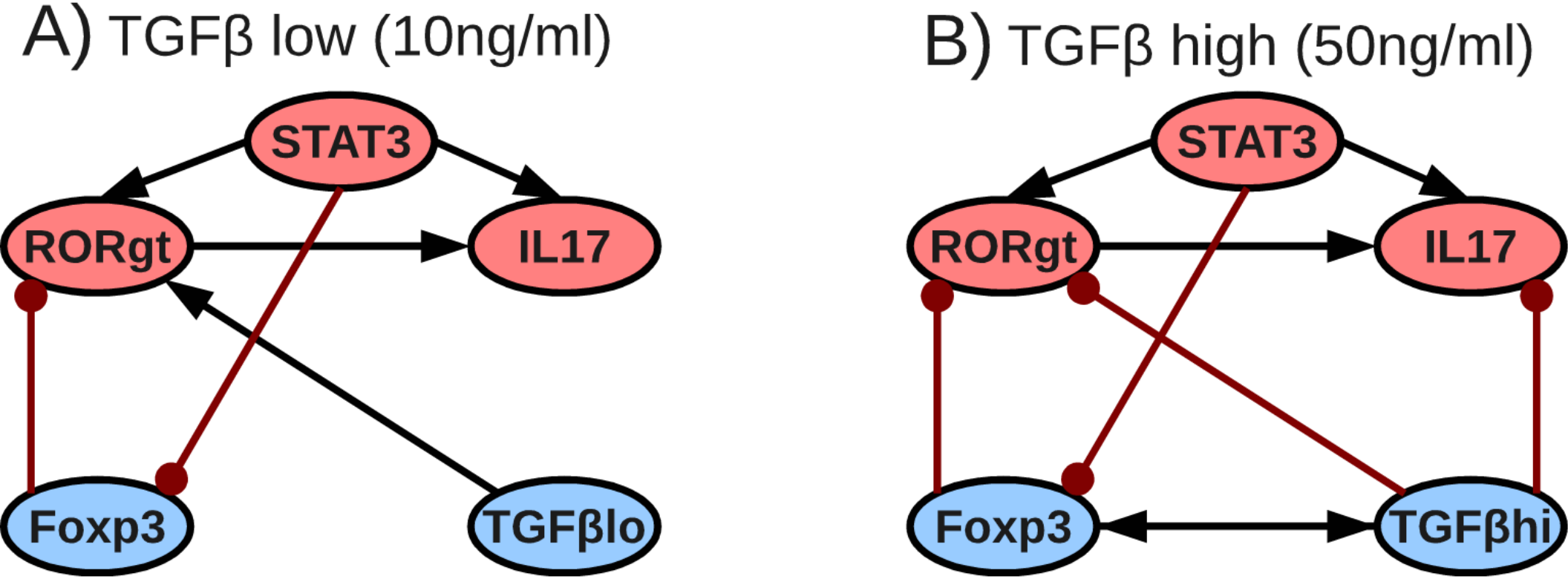
elementos aleatorios

activación genes

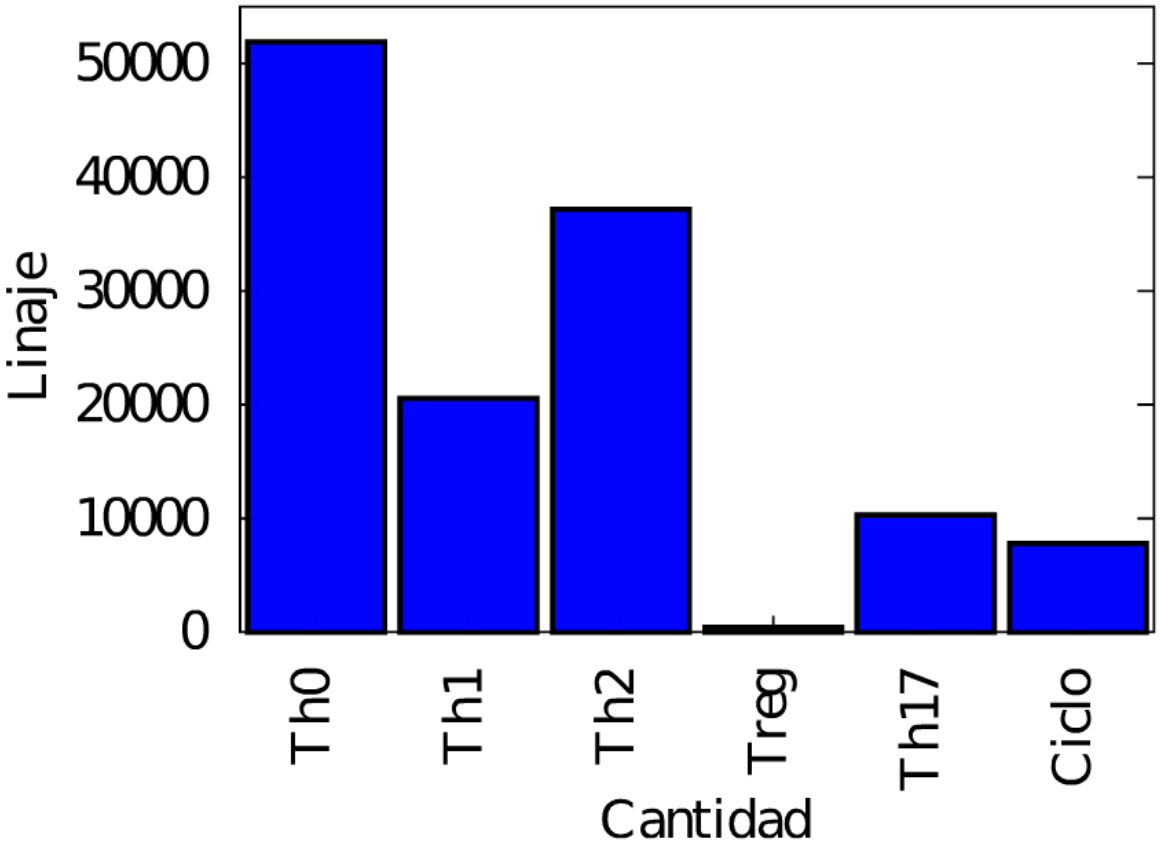
proteínas

tiempo

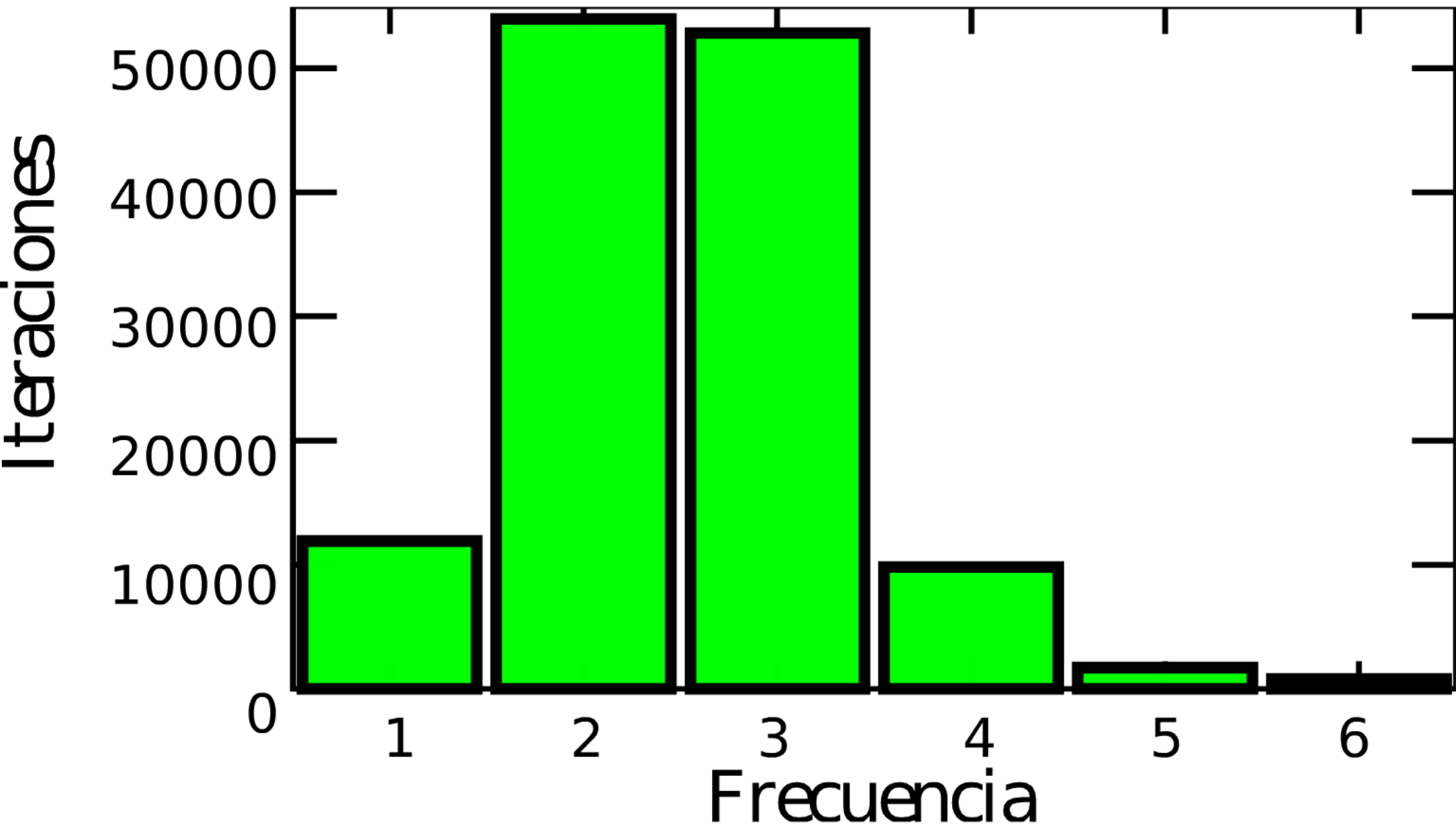

IL12
IL18
IL12R
IL18R
STAT4
IRAK4
SOCS3
SOCS1
IL1
IL1R
IRAK1
IL17
IL17R
ERK
IL6
IL6R
IL21
IL21R
IL23R
IL23
IFNγ
IFNγR
STAT1
SOCS5
T-bet
RORgt
STAT3
NFAT
TCR
STAT6
GATA3
Foxp3
NFAT
TCR
IL4R
IL4
STAT5
IL2R
IL2
SMAD
TGFβR
TGFβ

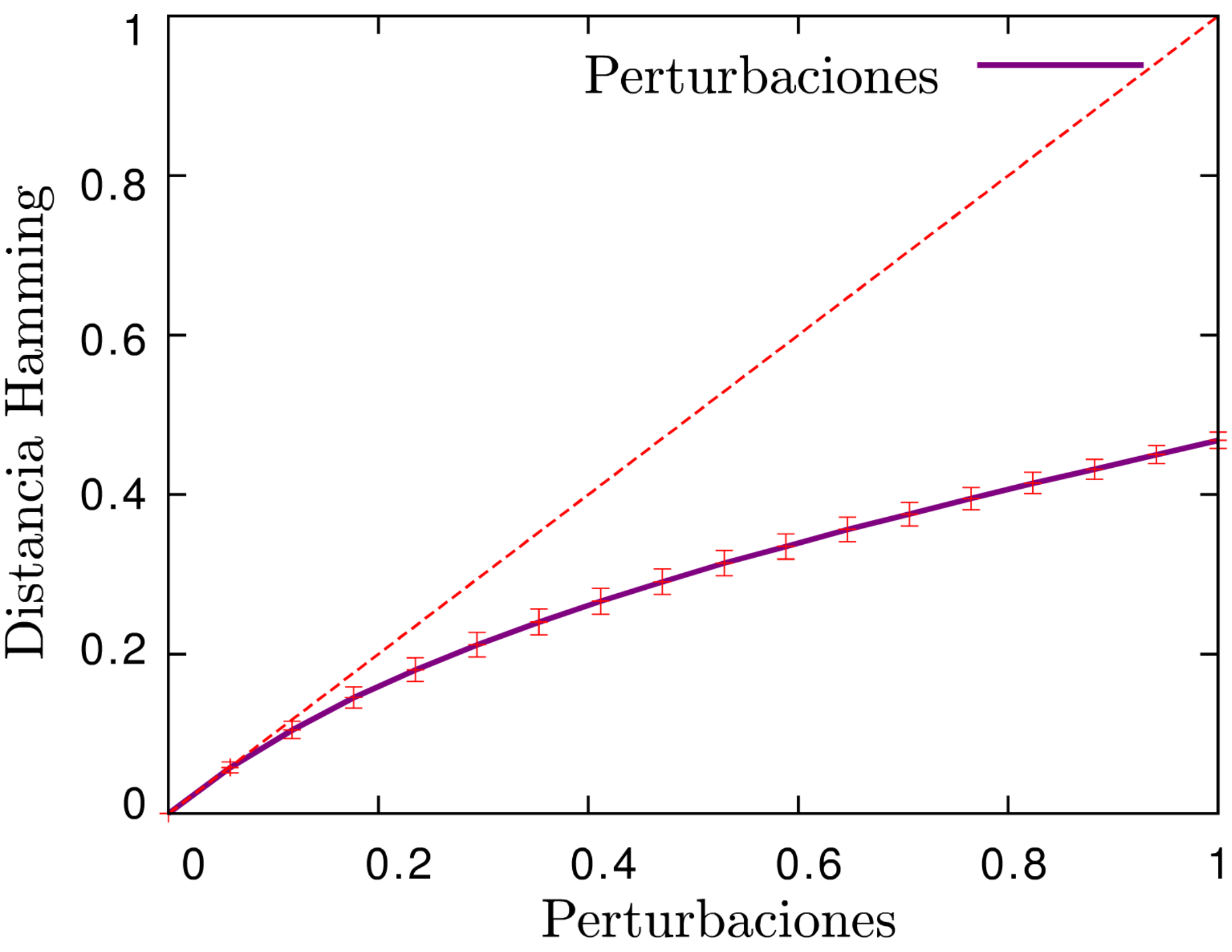

A) TGFβ low (10ng/ml)
STAT3
RORgt
IL17
Foxp3
TGFβlo
B) TGFβ high (50ng/ml)
STAT3
RORgt
IL17
Foxp3
TGFβhi

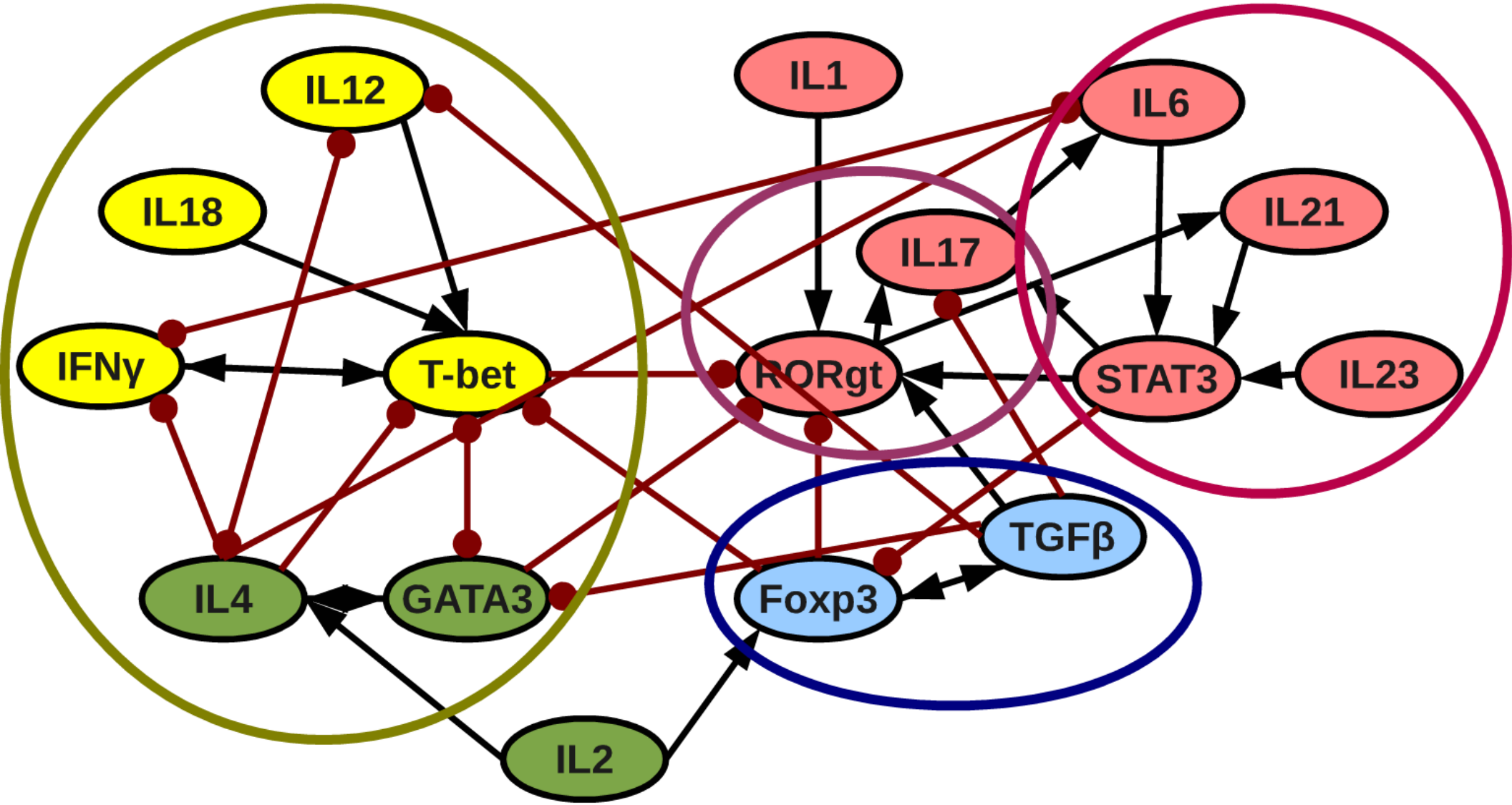
	Cantidad	Porcentaje
Puntos fijos	256	0.19
Ciclos	60	0.05
Transitivos	4355	3.32
Cúspides	126401	96.44
Estados totales	131072	100



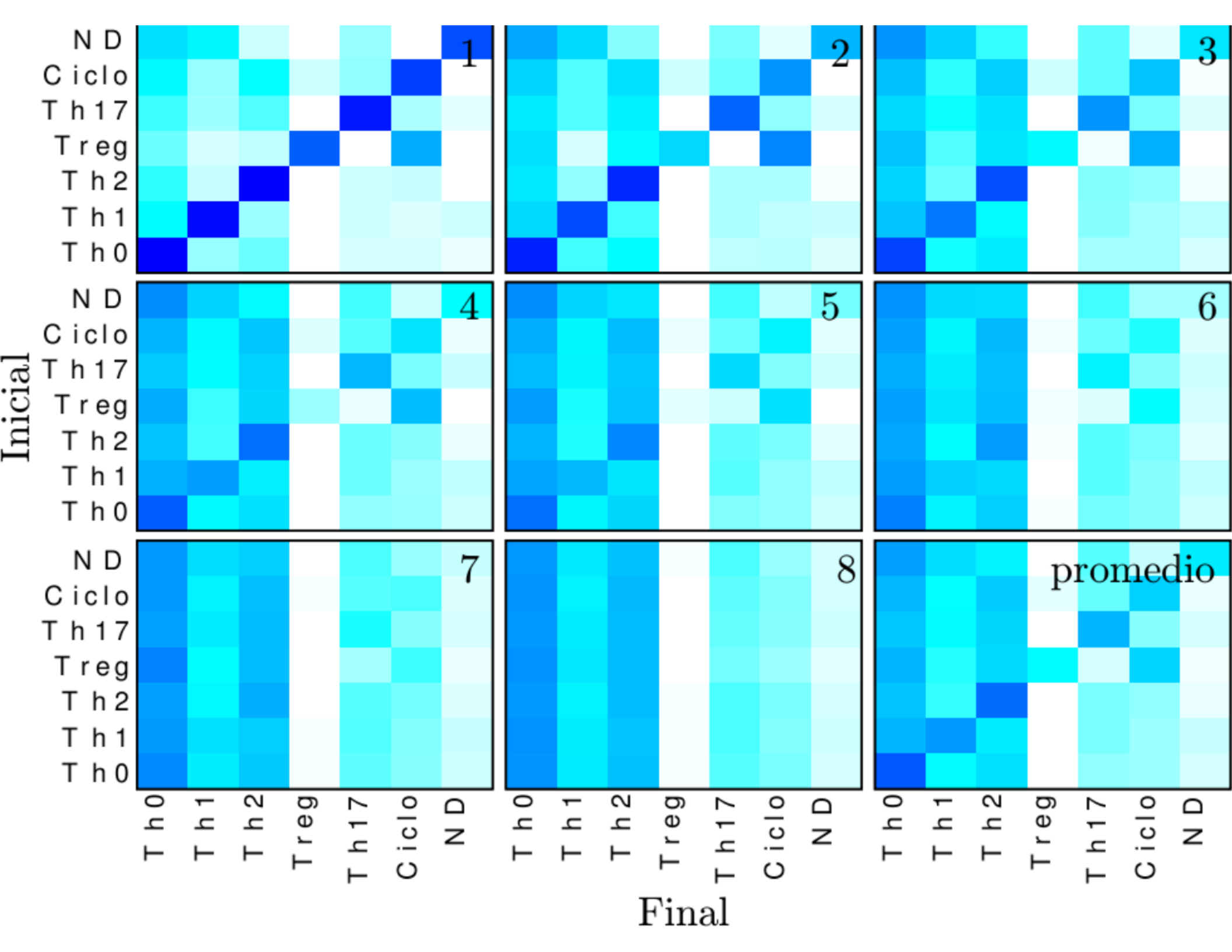
Inestable

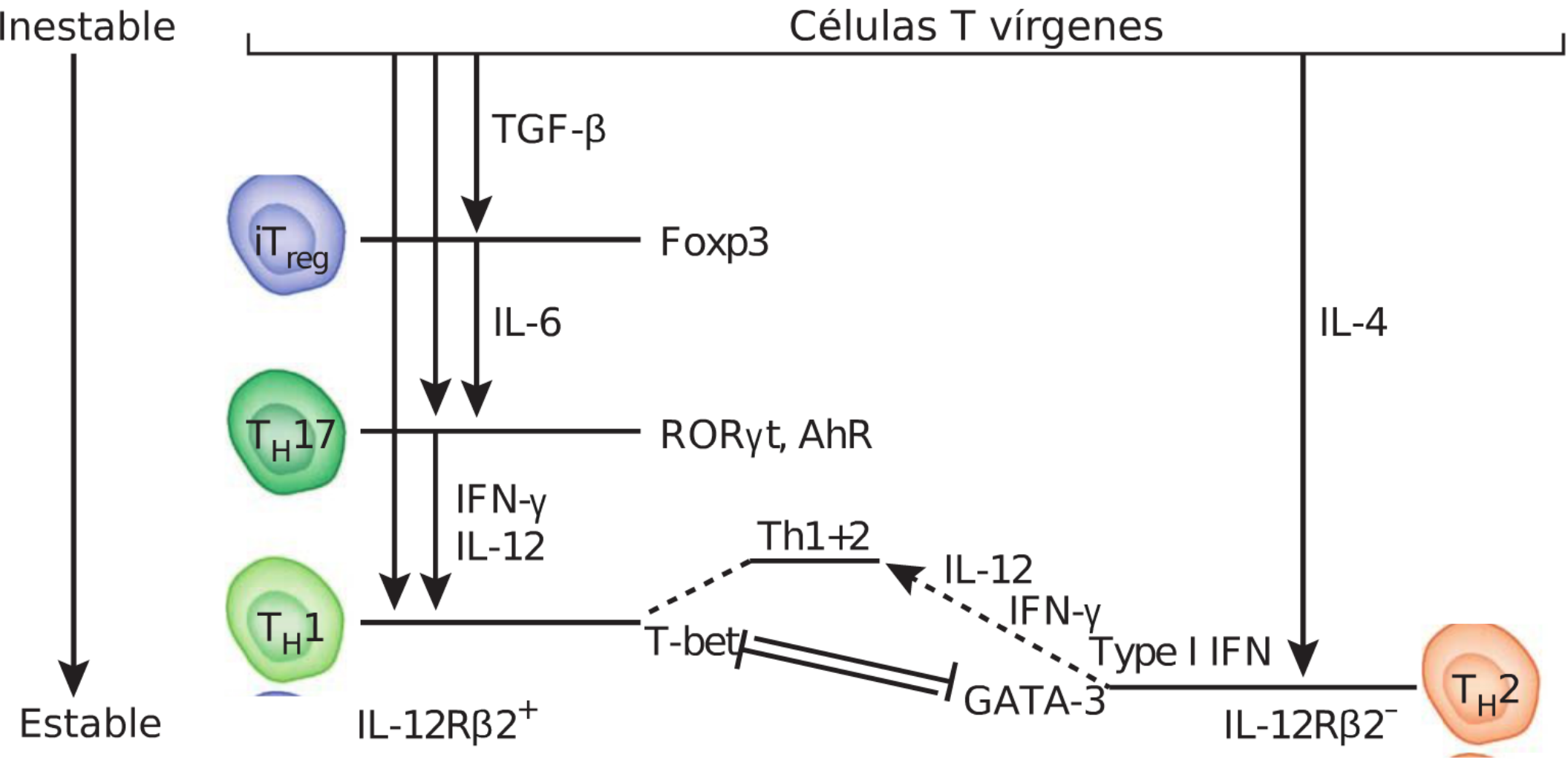

Iteraciones
50000
40000
30000
20000
10000
0
1
2
3
4
5
6
Frecuencia


Perturbaciones
Distancia Hamming
Perturbaciones
0
0.2
0.4
0.6
0.8
1
0
0.2
0.4
0.6
0.8
1


IL12
IL18
IFNγ
T-bet
IL4
GATA3
IL2
IL1
IL6
IL21
IL17
RORgt
STAT3
IL23
TGFβ
Foxp3

	Centralidad de grado	Centralidad de intermediación
TBET	0.69	0.11
IL4	0.63	0.05
GATA3	0.56	0.03
RORγt	0.56	0.1
IL12	0.5	0.04
IL6	0.44	0.09
TGFBhi	0.44	0.04
IFNg	0.38	0.1
IL21	0.38	0
FOXP3	0.38	0.05
TGFBlo	0.38	0
IL2	0.25	0
IL17	0.25	0.07
STAT3	0.25	0
IL18	0.19	0
IL1	0.19	0
IL23	0.06	0


1
2
3
4
5
6
7
8
promedio
N D
C iclo
T h17
T reg
T h2
T h1
T h0
Inicial
Final


Inestable
Células T vírgenes
TGF-β
iTreg
Foxp3
IL-6
IL-4
TH17
RORγt, AhR
IFN-γ
IL-12
Th1+2
IL-12
IFN-γ
TH1
T-bet
Type I IFN
GATA-3
TH2
Estable
IL-12Rβ2+
IL-12Rβ2−

Problemas

no discreto

plasticidad

TGF-B

señalización

constantes

población

proliferación

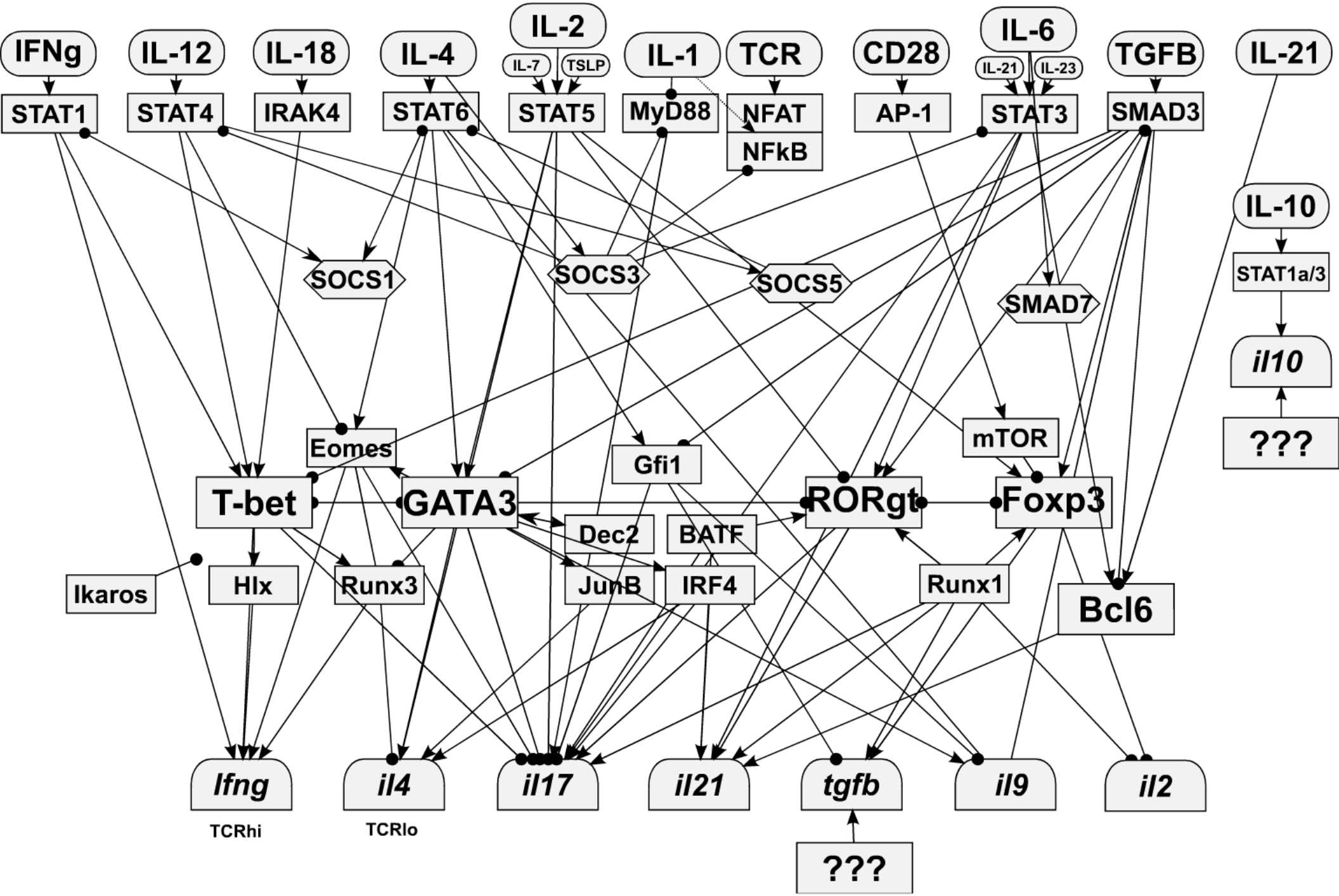
activación

Th0

células memoria

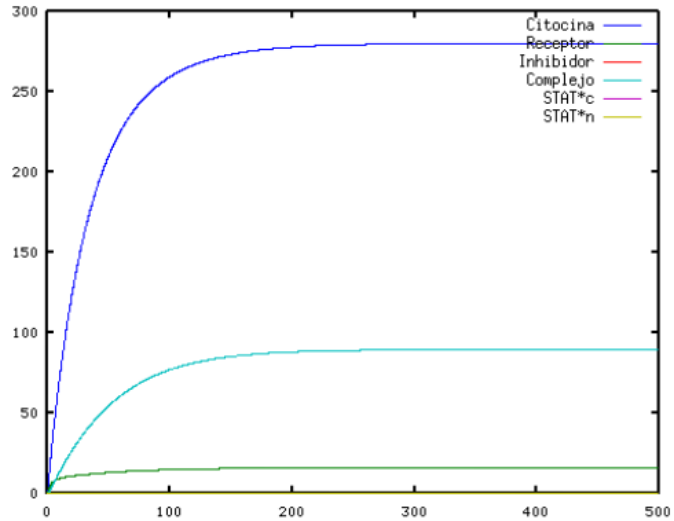
Treg

IL-10


IFNg
IL-12
IL-18
IL-4
IL-2
IL-7
TSLP
IL-1
TCR
CD28
IL-6
IL-21
IL-23
TGFB
IL-21
STAT1
STAT4
IRAK4
STAT6
STAT5
MyD88
NFAT
NFkB
AP-1
STAT3
SMAD3
IL-10
STAT1a/3
il10
???
SOCS1
SOCS3
SOCS5
SMAD7
Eomes
Gfi1
mTOR
T-bet
GATA3
RORgt
Foxp3
Dec2
BATF
Ikaros
Hlx
Runx3
JunB
IRF4
Runx1
Bcl6
Ifng
il4
il17
il21
tgfb
il9
il2
TCRhi
TCRlo
???

$$\frac{dC_L}{dt} = P_{ExtC} + P_{IntC} - k_{AsoCR} \cdot C_L \cdot R_L + k_{DisCR} \cdot CR - k_{DegC} \cdot C_L$$
$$\frac{dR_L}{dt} = P_{IntR} - k_{AsoCR} \cdot C_L \cdot R_L + k_{DisCR} \cdot CR - k_{DegR} \cdot R_L$$
$$\frac{dI_L}{dt} = P_{IntI} - k_{DegI} \cdot I_L$$
$$\frac{dCR}{dt} = k_{AsoCR} \cdot C_L \cdot R_L + k_{DisCR} \cdot CR$$
$$\frac{dS_C^*}{dt} = \frac{k_{cat} \cdot CR \cdot S}{k_m(1 + \frac{I}{k_I}) + S} - k_T \cdot S_C^*$$
$$\frac{dS_N^*}{dt} = k_T \cdot S_C^* \cdot \frac{V_{nuc}}{V_{Cit}} - K_{DP} \cdot S_N^*$$
$$\frac{dS}{dt} = P_{IntS} - k_{DegS} \cdot S - \frac{k_{cat} \cdot CR \cdot S}{k_m(1 + \frac{I}{k_I}) + S} = 0$$

$$Gen = g(ST_N^*, ...)$$
$$P_{Int} = f(Gen_1, ...)$$



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