

**Computational systems biophysics in health and disease at the molecular, cellular, and cell-population levels**

Jose Vilar



Biofisika Institute (CSIC, UPV/EHU),  
University of the Basque Country,  
Bilbao, Spain

1998-2004: Physics & Biology ( Postdoc at Princeton U./HHMI & Rockefeller U.)  
2004-2008: Computational Biology (Lab Head & Asst. Member at MSKCC)  
2008- : Biophysics (Ikerbasque Prof. at U. Basque Country)

**Goal:**

To understand and **accurately** predict the molecular, cellular, and cell-population behavior in terms of the interactions of the components and *vice versa*

**Outline:**

- Relevance of quantitative biophysical models
- Molecular level:
  - lac* operon
  - DNA looping, macromolecular assembly, and gene regulation
  - phage- $\lambda$
  - RXR
- Cellular level:
  - TGF- $\beta$  pathway
- Cell-population level:
  - T-cell apoptosis
  - Accurate diagnosis of acute myeloid leukemia

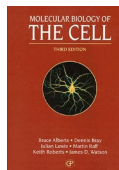
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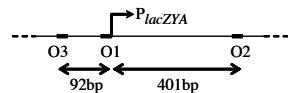
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**A physicist getting into biology: read the Alberts, let's model the *lac* operon**



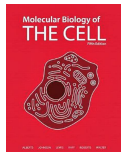
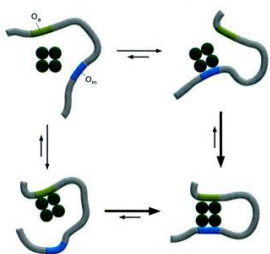
Molecular Biology of THE CELL, 3th ed (1994)

*lac* operon



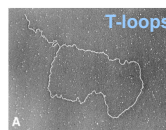
How come that O2 and O3 increase the repression level by a factor 60?  
Increase in the repressor local concentration around O1?  
But O2 and O3 are 10 and 300 times weaker than O1!

**Intuitive idea:**



Vilar & Leibler, J. Mol. Biol. 2003  
Figure from Alberts et al., Molecular Biology of THE CELL, 5th ed (2008)

**DNA looping**

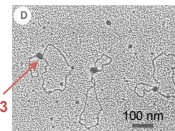


Griffith et al., 1999



Revet et al., 1999

- Bacteria: *lac*, *ara*, *gal*... (~200 bp)
- Viruses:  $\lambda$ -phage (~2,000 bp)
- Eukaryotes: transcription (~5,000 bp)
- p53, NF- $\kappa$ B, RXR
- mating type switching (~100,000 bp)
- (telomere)T-loops (~10,000bp)



Stenger et al., EMBO J 1994

### Modeling of DNA looping and transcription regulation (2 sites, 1 loop)

**State-oriented**

Key idea:  
 $\Delta G_{tv} = \Delta G_{binding1} + \Delta G_{binding2} + \Delta G_{looping}$

$P_k = \frac{1}{Z} [N]^k e^{-\Delta G_k / RT}$

Vilar & Leibler, J. Mol. Biol. 2003

**Domain-oriented**

$\Delta G(s) = (p + \epsilon_1)s_1 + (p + \epsilon_2)s_2 + (c_{12} - p s_1 s_2)s_L$   
 $p = p' - RT \ln[N]$

$P_s = \frac{1}{Z} e^{-\Delta G(s) / RT}$

Saiz & Vilar, Mol. Syst. Biol. 2006

### lac operon model:

**Free energy:**

$$\Delta G(s) = (p + \epsilon_1)s_1 + (p + \epsilon_2)s_2 + (p + \epsilon_3)s_3 + (c_{112} - p s_1 s_2)s_{L12} + (c_{113} - p s_1 s_3)s_{L13} + (c_{223} - p s_2 s_3)s_{L23}$$

**Transcription:**

$$\tau = \frac{1}{Z} \sum_s \tau_{max} (1 - s_1)(\chi s_3 + 1 - s_2) e^{-\Delta G(s) / RT}$$

There are no free parameters!

Exos. (symbols) by Oehler et al., 1990

Repression:  $\tau_{max} / \tau$

Repressor concentration (nM)

Saiz & Vilar, Nuc. Acids Res. 2008

### In vivo properties of DNA

Free energy of looping ( $\pm 0.15$  kcal/mol)

$$\Delta G_L = -RT \ln \frac{R_{loop} - R_{noloop}}{R_{noloop} - 1} [N]$$

Muller et al., 1996

Saiz, Rubi, and Vilar, PNAS 2005; Saiz & Vilar, COSB 2006 & PLoS One 2007

### Combinatorial complexity in phage-λ

The octamer does not exist in solution!

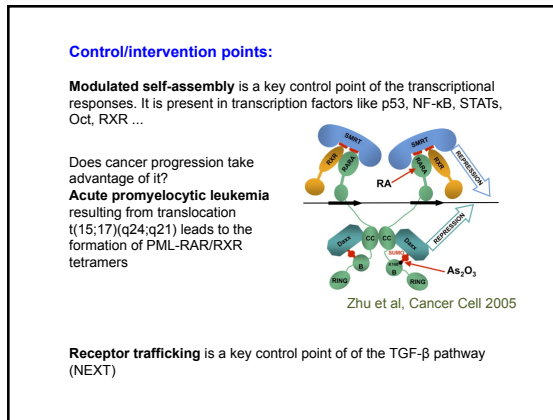
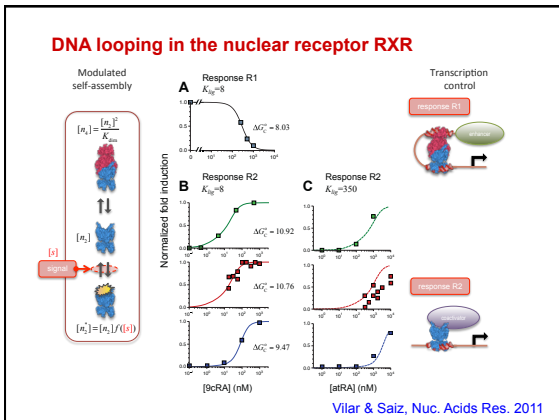
**cl & cro**  
 $2^3 \cdot 3^6 = 1458$  states  
 $1458 \cdot 13 = 18,954$  reactions

Saiz & Vilar, Mol. Syst. Biol. 2006

### Implementation in C++

```

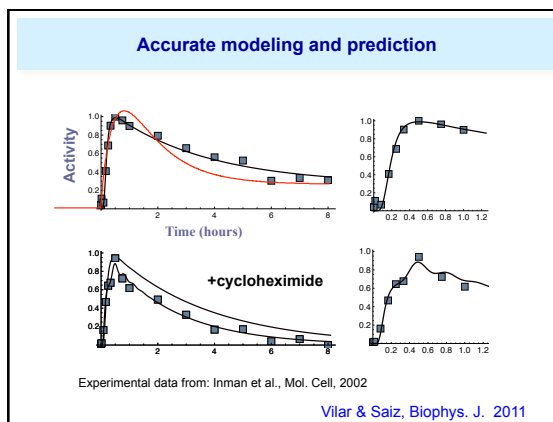
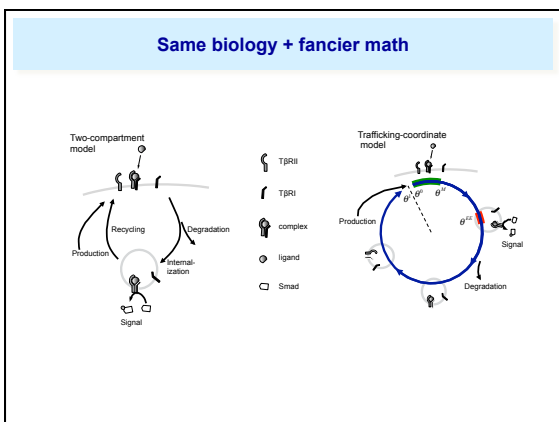
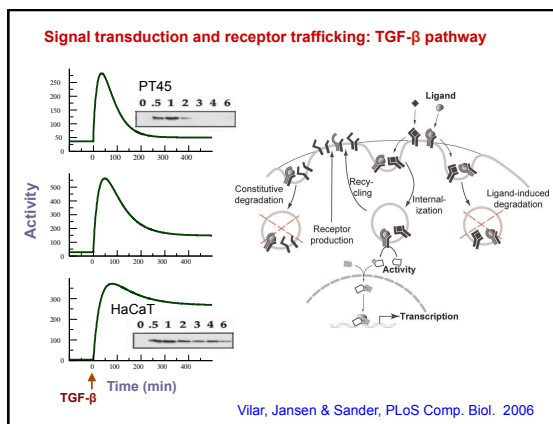
double H(long *s) {
    return
    -0.67*mylog(cro2[s]*1.47e-6)/nsbfactor(CI2)*[s[0]*1]+[s[2]*1]+[s[3]*1]+[s[4]*1]+[s[5]*1]+[s[6]*1]+[s[7]*1]+[s[8]*1]+[s[9]*1]+[s[10]*1]+[s[11]*1]+[s[12]*1]+[s[13]*1]+[s[14]*1]+[s[15]*1]+[s[16]*1]+[s[17]*1]+[s[18]*1]+[s[19]*1]+[s[20]*1]+[s[21]*1]+[s[22]*1]+[s[23]*1]+[s[24]*1]+[s[25]*1]+[s[26]*1]+[s[27]*1]+[s[28]*1]+[s[29]*1]+[s[30]*1]+[s[31]*1]+[s[32]*1]+[s[33]*1]+[s[34]*1]+[s[35]*1]+[s[36]*1]+[s[37]*1]+[s[38]*1]+[s[39]*1]+[s[40]*1]+[s[41]*1]+[s[42]*1]+[s[43]*1]+[s[44]*1]+[s[45]*1]+[s[46]*1]+[s[47]*1]+[s[48]*1]+[s[49]*1]+[s[50]*1]+[s[51]*1]+[s[52]*1]+[s[53]*1]+[s[54]*1]+[s[55]*1]+[s[56]*1]+[s[57]*1]+[s[58]*1]+[s[59]*1]+[s[60]*1]+[s[61]*1]+[s[62]*1]+[s[63]*1]+[s[64]*1]+[s[65]*1]+[s[66]*1]+[s[67]*1]+[s[68]*1]+[s[69]*1]+[s[70]*1]+[s[71]*1]+[s[72]*1]+[s[73]*1]+[s[74]*1]+[s[75]*1]+[s[76]*1]+[s[77]*1]+[s[78]*1]+[s[79]*1]+[s[80]*1]+[s[81]*1]+[s[82]*1]+[s[83]*1]+[s[84]*1]+[s[85]*1]+[s[86]*1]+[s[87]*1]+[s[88]*1]+[s[89]*1]+[s[90]*1]+[s[91]*1]+[s[92]*1]+[s[93]*1]+[s[94]*1]+[s[95]*1]+[s[96]*1]+[s[97]*1]+[s[98]*1]+[s[99]*1]+[s[100]*1]+[s[101]*1]+[s[102]*1]+[s[103]*1]+[s[104]*1]+[s[105]*1]+[s[106]*1]+[s[107]*1]+[s[108]*1]+[s[109]*1]+[s[110]*1]+[s[111]*1]+[s[112]*1]+[s[113]*1]+[s[114]*1]+[s[115]*1]+[s[116]*1]+[s[117]*1]+[s[118]*1]+[s[119]*1]+[s[120]*1]+[s[121]*1]+[s[122]*1]+[s[123]*1]+[s[124]*1]+[s[125]*1]+[s[126]*1]+[s[127]*1]+[s[128]*1]+[s[129]*1]+[s[130]*1]+[s[131]*1]+[s[132]*1]+[s[133]*1]+[s[134]*1]+[s[135]*1]+[s[136]*1]+[s[137]*1]+[s[138]*1]+[s[139]*1]+[s[140]*1]+[s[141]*1]+[s[142]*1]+[s[143]*1]+[s[144]*1]+[s[145]*1]+[s[146]*1]+[s[147]*1]+[s[148]*1]+[s[149]*1]+[s[150]*1]+[s[151]*1]+[s[152]*1]+[s[153]*1]+[s[154]*1]+[s[155]*1]+[s[156]*1]+[s[157]*1]+[s[158]*1]+[s[159]*1]+[s[160]*1]+[s[161]*1]+[s[162]*1]+[s[163]*1]+[s[164]*1]+[s[165]*1]+[s[166]*1]+[s[167]*1]+[s[168]*1]+[s[169]*1]+[s[170]*1]+[s[171]*1]+[s[172]*1]+[s[173]*1]+[s[174]*1]+[s[175]*1]+[s[176]*1]+[s[177]*1]+[s[178]*1]+[s[179]*1]+[s[180]*1]+[s[181]*1]+[s[182]*1]+[s[183]*1]+[s[184]*1]+[s[185]*1]+[s[186]*1]+[s[187]*1]+[s[188]*1]+[s[189]*1]+[s[190]*1]+[s[191]*1]+[s[192]*1]+[s[193]*1]+[s[194]*1]+[s[195]*1]+[s[196]*1]+[s[197]*1]+[s[198]*1]+[s[199]*1]+[s[200]*1]+[s[201]*1]+[s[202]*1]+[s[203]*1]+[s[204]*1]+[s[205]*1]+[s[206]*1]+[s[207]*1]+[s[208]*1]+[s[209]*1]+[s[210]*1]+[s[211]*1]+[s[212]*1]+[s[213]*1]+[s[214]*1]+[s[215]*1]+[s[216]*1]+[s[217]*1]+[s[218]*1]+[s[219]*1]+[s[220]*1]+[s[221]*1]+[s[222]*1]+[s[223]*1]+[s[224]*1]+[s[225]*1]+[s[226]*1]+[s[227]*1]+[s[228]*1]+[s[229]*1]+[s[230]*1]+[s[231]*1]+[s[232]*1]+[s[233]*1]+[s[234]*1]+[s[235]*1]+[s[236]*1]+[s[237]*1]+[s[238]*1]+[s[239]*1]+[s[240]*1]+[s[241]*1]+[s[242]*1]+[s[243]*1]+[s[244]*1]+[s[245]*1]+[s[246]*1]+[s[247]*1]+[s[248]*1]+[s[249]*1]+[s[250]*1]+[s[251]*1]+[s[252]*1]+[s[253]*1]+[s[254]*1]+[s[255]*1]+[s[256]*1]+[s[257]*1]+[s[258]*1]+[s[259]*1]+[s[260]*1]+[s[261]*1]+[s[262]*1]+[s[263]*1]+[s[264]*1]+[s[265]*1]+[s[266]*1]+[s[267]*1]+[s[268]*1]+[s[269]*1]+[s[270]*1]+[s[271]*1]+[s[272]*1]+[s[273]*1]+[s[274]*1]+[s[275]*1]+[s[276]*1]+[s[277]*1]+[s[278]*1]+[s[279]*1]+[s[280]*1]+[s[281]*1]+[s[282]*1]+[s[283]*1]+[s[284]*1]+[s[285]*1]+[s[286]*1]+[s[287]*1]+[s[288]*1]+[s[289]*1]+[s[290]*1]+[s[291]*1]+[s[292]*1]+[s[293]*1]+[s[294]*1]+[s[295]*1]+[s[296]*1]+[s[297]*1]+[s[298]*1]+[s[299]*1]+[s[300]*1]+[s[301]*1]+[s[302]*1]+[s[303]*1]+[s[304]*1]+[s[305]*1]+[s[306]*1]+[s[307]*1]+[s[308]*1]+[s[309]*1]+[s[310]*1]+[s[311]*1]+[s[312]*1]+[s[313]*1]+[s[314]*1]+[s[315]*1]+[s[316]*1]+[s[317]*1]+[s[318]*1]+[s[319]*1]+[s[320]*1]+[s[321]*1]+[s[322]*1]+[s[323]*1]+[s[324]*1]+[s[325]*1]+[s[326]*1]+[s[327]*1]+[s[328]*1]+[s[329]*1]+[s[330]*1]+[s[331]*1]+[s[332]*1]+[s[333]*1]+[s[334]*1]+[s[335]*1]+[s[336]*1]+[s[337]*1]+[s[338]*1]+[s[339]*1]+[s[340]*1]+[s[341]*1]+[s[342]*1]+[s[343]*1]+[s[344]*1]+[s[345]*1]+[s[346]*1]+[s[347]*1]+[s[348]*1]+[s[349]*1]+[s[350]*1]+[s[351]*1]+[s[352]*1]+[s[353]*1]+[s[354]*1]+[s[355]*1]+[s[356]*1]+[s[357]*1]+[s[358]*1]+[s[359]*1]+[s[360]*1]+[s[361]*1]+[s[362]*1]+[s[363]*1]+[s[364]*1]+[s[365]*1]+[s[366]*1]+[s[367]*1]+[s[368]*1]+[s[369]*1]+[s[370]*1]+[s[371]*1]+[s[372]*1]+[s[373]*1]+[s[374]*1]+[s[375]*1]+[s[376]*1]+[s[377]*1]+[s[378]*1]+[s[379]*1]+[s[380]*1]+[s[381]*1]+[s[382]*1]+[s[383]*1]+[s[384]*1]+[s[385]*1]+[s[386]*1]+[s[387]*1]+[s[388]*1]+[s[389]*1]+[s[390]*1]+[s[391]*1]+[s[392]*1]+[s[393]*1]+[s[394]*1]+[s[395]*1]+[s[396]*1]+[s[397]*1]+[s[398]*1]+[s[399]*1]+[s[400]*1]+[s[401]*1]+[s[402]*1]+[s[403]*1]+[s[404]*1]+[s[405]*1]+[s[406]*1]+[s[407]*1]+[s[408]*1]+[s[409]*1]+[s[410]*1]+[s[411]*1]+[s[412]*1]+[s[413]*1]+[s[414]*1]+[s[415]*1]+[s[416]*1]+[s[417]*1]+[s[418]*1]+[s[419]*1]+[s[420]*1]+[s[421]*1]+[s[422]*1]+[s[423]*1]+[s[424]*1]+[s[425]*1]+[s[426]*1]+[s[427]*1]+[s[428]*1]+[s[429]*1]+[s[430]*1]+[s[431]*1]+[s[432]*1]+[s[433]*1]+[s[434]*1]+[s[435]*1]+[s[436]*1]+[s[437]*1]+[s[438]*1]+[s[439]*1]+[s[440]*1]+[s[441]*1]+[s[442]*1]+[s[443]*1]+[s[444]*1]+[s[445]*1]+[s[446]*1]+[s[447]*1]+[s[448]*1]+[s[449]*1]+[s[450]*1]+[s[451]*1]+[s[452]*1]+[s[453]*1]+[s[454]*1]+[s[455]*1]+[s[456]*1]+[s[457]*1]+[s[458]*1]+[s[459]*1]+[s[460]*1]+[s[4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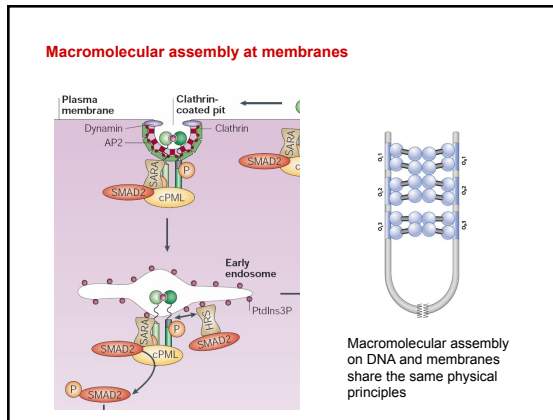
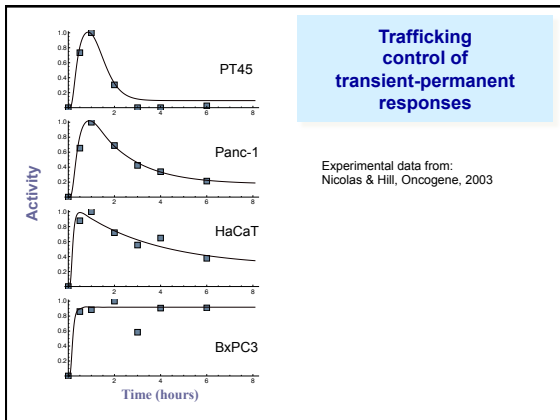


**Goal:**  
 To understand and accurately predict the molecular, cellular, and cell-population behavior in terms of the interactions of the components and vice versa

**Outline:**

- Relevance of quantitative biophysical models
- Molecular level:
  - lac operon
  - DNA looping, macromolecular assembly, and gene regulation
  - phage-λ
  - RXR
- Cellular level:
  - TGF-beta pathway
- Cell-population level:
  - T-cell apoptosis
  - Accurate diagnosis of acute myeloid leukemia

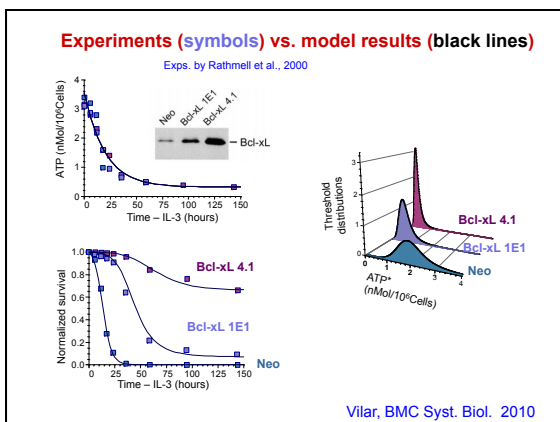
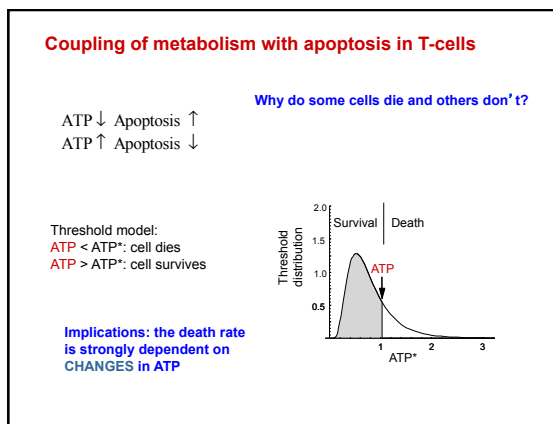




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### Best Performer method at the DREAM6/FlowCAP2 Molecular Classification of Acute Myeloid Leukemia Challenge

The goal of this challenge is to diagnose Acute Myeloid Leukemia from patient samples using flow cytometry data

The samples consist of 43 AML positive patients and 316 healthy donors. Samples from peripheral blood or bone marrow aspirate were collected over a one year period

Information for about half of the donors on whether they are healthy or AML positive is provided as training set

The challenge is to determine the state of health of the other half, based only on the provided flow cytometry data

Vilar, Phys. Rev. X 2014

### DREAM6/FlowCAP2 AML diagnosis challenge

	FL1	FL2	FL3	FL4	FL5
<b>Tube 1</b>	IgG1-FITC	IgG1-PE	CD45-ECD	IgG1-PC5	IgG1-PC7
<b>Tube 2</b>	Kappa-FIT	Lambda-PE	CD45-ECD	CD19-PC5	CD20-PC7
<b>Tube 3</b>	CD7-FITC	CD4-PE	CD45-ECD	CD8-PC5	CD2-PC7
<b>Tube 4</b>	CD15-FITC	CD13-PE	CD45-ECD	CD16-PC5	CD56-PC7
<b>Tube 5</b>	CD14-FITC	CD11c-PE	CD45-ECD	CD64-PC5	CD33-PC7
<b>Tube 6</b>	HLA-DR-FITC	CD117-PE	CD45-ECD	CD34-PC5	CD38-PC7
<b>Tube 7</b>	CD5-FITC	CD19-PE	CD45-ECD	CD3-PC5	CD10-PC7
<b>Tube 8</b>	Non Specific	Non Specific	Non Specific	Non Specific	Non Specific

Key points to distinguish between **AML** and **Normal** cases:

- 1) How to look at the distributions
- 2) What to look at

### Entropies for comparing distributions

Gibbs entropy formula:

$$S = S_{eq} - k_B \int P(\Gamma) \ln \frac{P(\Gamma)}{P_{eq}(\Gamma)} d\Gamma \quad \text{Entropy is maximum when } P=P_{eq}$$

Entropies with respect to AML and Normal states:

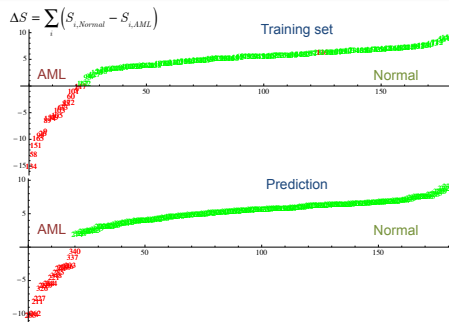
$$S_{i,AML} = - \int P_i(\Gamma) \ln \frac{P_i(\Gamma)}{P_{AML}(\Gamma)} d\Gamma \quad S_{i,Normal} = - \int P_i(\Gamma) \ln \frac{P_i(\Gamma)}{P_{Normal}(\Gamma)} d\Gamma$$

Entropy difference:

$$\Delta S_i = S_{i,Normal} - S_{i,AML} = \int P_i(\Gamma) \ln \frac{P_{Normal}(\Gamma)}{P_{AML}(\Gamma)} d\Gamma$$

It is **positive** for  $P=P_{Normal}$  and **negative** for  $P=P_{AML}$ .

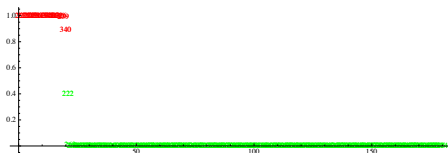
### 4D entropies (FL 2,3,4,5),(FL 1,2,3,4)x(Tb 3,4,5,6)



### Scores

Probability AML

$$P_{AML} = \frac{1}{e^{\Delta S} + 1}$$



### Take-home messages:

Piecing back together all the genetic, biochemical, molecular, and structural information into a physiologically relevant description of the cell, needs "constructive" methods.

Computational biophysics has emerged as a promising tool for transforming molecular detail into a more integrated form of understanding complex behavior.

Having a global view of the processes involved and their effects through all relevant levels of biological organization is crucial to identify and characterize the **key control elements** of the system.