Immunoinformatics
-
Computational Immunology
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• Summary
Immune System Presentation
Immune System

• Composed of many interdependent
  – cell types
  – organs

• Collectively protect the body
Self/Non-Self

• Every cell display a marker based on the major histocompatibility complex (MHC)
• MHC may be of three different classes
  – MHC I, MHC II, MHC III
• Any cell not displaying this marker is treated as non-self and attacked.
Main Organs

- **Bone Marrow**
  - Immune system’s cells production
- **Thymus**
  - Maturation of T cells
- **Spleen**
  - Immunologic blood filter and RBC recycle unit
- **Lymph Nodes**
  - Immunologic filter for the lymph
Main Cells

- Blood cells are manufactured by stem cells in the bone marrow.
- The process is called hematopoiesis.
- Three different types of blood cells:
  - Erythrocytes (RBC)
  - Leukocytes (WBC)
    - Granulocytes
    - Agranulocytes
  - Thrombocytes (platelets)
Main Cells (2)

- Megacaryocyte ___________________ platelets
- Proérythroblaste ___________________ erythrocyte
- Promonocyte _____ monocyte/macrophage
- Myeloide source ___________________ neutrophile
- Granulocyte
  - Eosinophile
  - Basophile
  - Mastocyte
- Pre-B cells
  - B cells
  - T-dependant
  - T-independant
- Pre-T cells
  - T helper
  - T killer

Stem cells:

- Ancestor cell
  - Ancestor lymphoid
  - Megakaryocyte
  - Proerythroblast
  - Promonocyte
  - Myeloide source
  - Granulocyte
  - Eosinophile
  - Basophile
  - Mastocyte
  - Pre-B cells
  - Pre-T cells

B cells
T-dependant
B cells
T-independant
T helper
T killer
Main Cells (3)

- Lymphocytes
  - T
    - TH (CD4+ T)
    - TK (CD8+ T)
  - B
  - NK
- Granulocytes
- Macrophages
- Dendritic Cells
Antibody

- **Antigen:** substance that elicits an immune response
- **Antibody:** complex protein secreted by B cells
  - Tagging: Coat the foreign invaders to make them attractive to the circulating scavenger cells
  - Complement fixation: Combine with antigens and a circulating protein in the blood that cause lysis
  - Neutralization: Coat viruses and prevent them from entering cells
  - Agglutination: massively clump to the antigen
  - Precipitation: force insolubility and settling out of solution
Antibody (2)

- IgG - 75%
- IgA - 15%
- IgM - 7.5%
- IgD - 1%
- IgE - 0.002%
Activation of WBC

Activation of helper T cells

Activation of cytotoxic T cells

Activation of B cells to make antibody
VIRUS IMMUNITY

- NK cells
- IFN-alpha
- IFN-beta
- NK cells
- B cells
- Antibody
- Cytokines
- Macrophage
- IL-2
- Bone marrow
- Cytokines
- Cytokines
BACTERIA IMMUNITY
Cell-mediated/Humoral Immunity

• Cell-mediated immunity
  – T cells (lymphocytes) bind to the surface of other cells that display the antigen and trigger a response. The response may involve
    – other lymphocytes and
    – any of the other WBC

• Humoral immunity
  – Antibodies, dissolved in blood, lymph, and other body fluids bind the antigen and trigger a response to it.
Innate/Acquired-Adaptive Immunity

• Innate immunity rely on a global distinction of self/non-self recognition
  – Instantaneous
  – Non specific
  – Non adaptative
  – Memory less

• Adaptative immunity involve the cell-mediated and hummoral response.
  – Time limited to the eradication of the antigen
  – Specific to the given antigen
  – Adaptative
  – Memory full
Immunologic Memory

• First Response (4-5 days)
  – First adaptive response against a given antigen

• Secondary Response (1 day)
  – Shorter lag time
  – More rapid buildup
  – Higher overall level of response
  – Better fit to the invading antigen
  – Utilizes IgG instead of IgM
Immunoinformatics

Chair’s introduction

Hans-George Rammensee

Immunoinformatics the new kid in town

Vladimir Brusic and Nikolai Petrovsky
3 Fields

• Theoretical immunology or immunoinformatics
  – Hard
    • Hard facts, can be verified by experience
  – Semi-soft
    • Algorithms and parameters used to ‘create’ the hard part
  – Soft
    • Can never be tested with hard facts
Combinatorial Science

• Immunoinformatics also known as computational immunology
• Astounding diversity of immune system components
• Complexity of the regulatory pathways
• Complexity of the network-type interactions
Immunology Databases

• Management and analysis of immunological data plays a major role in immunoinformatics
• The appropriate use of informatics technique greatly improve the efficiency of immunology research
Standards

• Data Standards
  – IUPAC/IUBMB
  – Gene ontology consortium
  – Immunogenetics ontologies and nomenclature for immunoglobulins

• Data quality

• Accuracy of computational methods
IMGT, the international ImMunoGeneTics information system

Marie-Paule Lefranc
Université de Montpellier II
IMGT Databases

- IMGT/LIGM_DB
- IMGT/3Dstructure-DB
- IMGT/MHC_DB
- IMGT/PRIMER-DB
- IMGT/GENE-DB
IMGT Databases (2)

- IMGT/LIGM-DB
  - 75000 nucleotide sequences from 105 species
- 6 people working full time on annotation
- Daily updates and curation
- Multilevel annotation
- Standardized keywords
IMGT Databases (3)

- Distributed by anonymous FTP
  - CINES, EBI, IGH, Institut Pasteur, ...
  - Flat files

- BLAST and FASTA searchable

- Relational Database Structure
  - Sybase for LIGM, GENE and PROTEIN
  - MySQL for 3DStructure and PRIMER

- IMGT API
IMGT Web Resources

• IMGT Scientific chart
  – Standardized keywords
  – Standardized sequence annotation
  – Standardized IG and TR gene nomenclature
• IMGT Repertoire
• IMGT/V-QUEST
• IMGT/JunctionAnalysis
• IMGT-ONTOLOGY
IMGT/PhyloGene tree with branch lengths

The phylogenetic tree found by NJ from your selected sequences and rooted using the midpoint procedure is the following:

- IGHV7-31*01 AB019437 Homo sapiens
- IGHV15S1*01 U39293 Mus musculus
  - IGHV4-4*01 Z12357 Homo sapiens
  - IGHV5-1*01 J04097 Homo sapiens
    - IGHV517*01 U04227 Mus musculus
    - IGHV513*01 AF290972 Mus musculus

- Display the same tree without branch lengths
- Root this tree using an outgroup
- Root this tree using the midpoint method
- Return to the sequence selection (to add an outgroup for example)
- Download the tree in Newick format
Discussion

• Data mining through multiple databases
• Database Access
• SRS
• Webservices
• Workflows
Available Databases

- **EMBOSS Results**
- **Sequence databanks - complete**
  - EMBL
  - RefSeq
  - RefSeq Protein
  - TREMBL
  - SWALL
  - SWISSPROT
  - PIR
  - REMTREMBL
  - UniProt
  - IPI
  - ENSEMBL
- **Sequence databanks - subsections**
  - Related
    - PROSITE
    - PROSITE DOC
    - PRINTS
    - PFAM
    - PFAMB
    - SWISSPFAM
    - PFAMHMM
    - PFAMSEED
    - EPD
    - DBEST
    - UNIGENE
    - UNIGENE SEQ
    - UNIGENE UNIQ
    - INTERPRO
    - IPR MATCHES
    - MARKERS
    - MARKERSHO
    - MARKERSLO
- **Tool Results**
- **Protein3DStruct**
  - PDB
  - PDB FINDER
- **Genome**
  - LOCUS LINK
- **Mutations**
  - OMIM
- **Metabolic Pathways**
  - ENZYME
  - PATHWAY
  - LENZYME
  - LCOMPOUND
  - LREACTION
- **Others**
  - TAXONY
  - GENETIC CODE
  - REBASE
  - AA INDEX
  - AA MATRIX
Web Services Description Language (WSDL), a standard method of describing Web Services and their capabilities. The following is a list of WSDL URLs:

<table>
<thead>
<tr>
<th>Service</th>
<th>URL</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSDbfetch</td>
<td><a href="http://www.ebi.ac.uk/ws/services/urn:Dbfetch?wsdl">http://www.ebi.ac.uk/ws/services/urn:Dbfetch?wsdl</a></td>
</tr>
<tr>
<td>WSFasta</td>
<td><a href="http://www.ebi.ac.uk/ws/WSFasta.wsdl">http://www.ebi.ac.uk/ws/WSFasta.wsdl</a></td>
</tr>
<tr>
<td>WSWUBlast</td>
<td><a href="http://www.ebi.ac.uk/ws/WSWUBlast.wsdl">http://www.ebi.ac.uk/ws/WSWUBlast.wsdl</a></td>
</tr>
<tr>
<td>WSLInterProScan</td>
<td><a href="http://www.ebi.ac.uk/ws/WSInterProScan.wsdl">http://www.ebi.ac.uk/ws/WSInterProScan.wsdl</a></td>
</tr>
</tbody>
</table>
The future of computational modelling and prediction systems in clinical immunology

Nikolai Petrovsky, Diego Silva and Vladimir Brusic
Immunoinformatics In Improving Transplantation Outcomes

- ANN 6 month graft survival prediction
  - MLFF (3 layer feed forward) Neural Network
    - 84.95% accuracy for successful transplants
    - 71.70% accuracy for unsuccessful transplants

- Useful clinical tool improving transplantation outcome
- Acceptance by clinicians
ANN Neuron Model

- Input: external stimuli
- Weight: determine the contribution of each entry
- Threshold: bias value, may be seen as a supplementary input value with value -1.

\[ y = f\left(\sum_{i=1}^{n} w_i x_i - u\right) = f\left(\sum_{i=0}^{n} w_i x_i\right) \]
Human Immune Disease-Gene Identification

• Orthologues genes identification
  – Mouse vs Human

• RIKEN database

• FANTOM 3

• Orthogonal gene search
Antigen Presentation Pathways

- TAP (Transporter Associated with antigen Processing)
- HLA-binding peptides with affinity to TAP
  - 15% for HLA-B*5401
  - 100% for HLA-B*2703
Prediction Of Allergeneicity

- Allergenic potential aspect:
  - allergenic Immunogenicity
    - Likelihood of an IgE or T cell response to a particular allergen
  - Cross-reactivity
    - Ability of an IgE clonotype or a T cell clone, which was previously induced by one allergen, to react with another allergen

- Allergens database
- Structural bioinformatics
- Homologue sequence search
Discussion

• Immunoinformatics accelerate the knowledge acquisition in clinical immunology
• Bioinformatics has broad applicability to immunology
• Development of *in-silico* models of entire systems – towards a virtual immune system
Summary

• Immunoinformatic is very complex and can be seen as a combinatorial science
• Available data come at an exponential rate
• Immunoinformatic rely on data and discoveries from other bioinformatics domains and informatic
• Workflow may become very important in the future
• Semantic is very important; XML may be very useful
• Clinical use of immunoinformatic solutions may be difficult to get accepted
References

• Books
  – Le Livre Blanc de l'Immunologie Médicale Société Française d'Immunologie, 1996
  – Cours d’immunologie du Dr. Chevailler, Faculté de Médecine d’Anger
  – Introduction à l’immunologie, Fischberg-Azimi, Université de Genève