From Systems Biology to Systems Medicine

Eudipharm Seminar: Model - Based Medicines Development
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Characteristics of Integrative Systems Biology

Considers the (emerging) properties and the dynamic behaviour of a biological system as different (more or less) from those of its interacting (elementary or modular) components

Combines exploratory investigations of global datasets with formalized hypotheses and question driven inquiries

Aims at identifying the necessary and sufficient characteristics enabling understanding (explaining and predicting) and piloting of the behaviour of biological systems in normal (evolutionary, developmental, physiological) and perturbed (environmental changes, disease, experimental) conditions
The Iterative Process of Integrative Systems Biology

1- Formulate and formalize a (general or particular) question

2- Define the components of an appropriate biological system and collect targeted and global data sets

3- Integrate them into an initial model of the system

4- Perturb systematically the system components (experimentally and through simulation) and study the results

5- Compare the responses observed to those predicted by the model

6- Refine the model so that its predictions fit better with the experimental observations

7- Design and test new perturbations allowing arbitration between multiple competing hypotheses

8- Iterate the process until an answer to the initial question is obtained
The Iterative Process of Integrative Systems Biology

« Middle-out » scheme for the study of biological systems
Modelling in Integrative Systems Biology

System / Component
Complex / Elementary
Pathway / Network
Function / Mechanism
Static / Dynamic

Linear / Non-linear
Deterministic / Stochastic
Precise / Fuzzy
Discrete / Continuous
Digital / Analogic

Abstract / Concrete
Graphical / Mathematical
Descriptive / Predictive
Causative / Correlative
Hierarchical / Self-organised
Modelling in Integrative Systems Biology

Experimental design, statistical power

Text and data mining, quality indices

Integration of heterogeneous data

Model construction, verification, refinement

Model analysis: sensitivity, bifurcation, stability, control

Numerical simulation, process calculi

Modularity, redundancy, robustness, fragility
European Science Foundation Forward Look
Systems Biology: a Grand Challenge for Europe

Olaf Wolkenhauer, University of Rostock
European Science Foundation Forward Look
Systems Biology: a Grand Challenge for Europe

Ursula Klingmüller, DKFZ, Heidelberg
The Grand Challenge of Integrative Systems Biology: Multiscale Integration

Multiple formalisms are used to model biological systems at their different levels of organization.

Molecular: e.g. ordinary and partial differential equations

Cellular: e.g. logical and Boolean networks, cellular automata

Organ: e.g. finite element lattices

They are often based on incompatible principles.

There is a need for an extended mathematical framework to enable multiscale integration across all levels simultaneously.
The Grand Challenge of Integrative Systems Biology: Multiscale Integration
Fourth principle
The theory of biological relativity

There is no privileged level of causality. This is necessarily true in systems possessing multiple levels interacting through ascending and descending feedback loops.

The fundamental concept is that, since all levels can be the starting point of a causal chain, each can be the basis for a simulation.

In biological systems, there is no privileged level dictating its law to the other levels. The levels are not equivalent, their relationships are not linear.
Systems medicine: the future of medical genomics and healthcare
Auffray, C., Chen, Z. and Hood, L.
(2009) Genome Medicine 1:2

Bridging the gap between systems biology and medicine
Clermont, G., Auffray, C. et al.
(2009) Genome Medicine 1:88

Systems medicine and integrated care to combat chronic noncommunicable diseases
Bousquet et al. (2011) Genome Medicine 3:43
Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

Innovative Medicines Initiative: Understanding Severe Asthma

Coordinator: Peter Sterk
University of Amsterdam
Severe asthma

Facts

– Despite all our attempts, the clinical course of severe asthma is far from optimal

– Unfortunately, the development of new drugs for severe asthma has not been successful during the past years

Reasons?

– Severe asthma is not a single disease: individual patients are clinically very different

– There are multiple and co-existent disease mechanisms

– At present the efficacy of new drugs cannot be predicted from preclinical models nor from currently defined patient characteristics
Bottlenecks in severe asthma

- Pathobiology
- Clinical phenotypes
- Clinical outcome
- Disease modification

- Predictive biomarkers
- Predictive preclinical models
- Predictive targets for intervention
Hypothesis

Biomarker fingerprints from high-dimensional molecular, physiological, and clinical data integrated by an innovative systems biology approach into distinct phenotype handprints will enable the prediction of clinical course and therapeutic efficacy, and identification of novel targets in the treatment of severe asthma.
Genes

Gene expression

Airway histology

Lung function

The patient

Respiratory Disease Phenotyping

Genetics
Epigenetics
Transcriptome
Proteome
Metabolome
Microbiome
Immunity
Inflammation
Remodeling
Responsiveness
Obstruction
Symptoms
Co-morbidity
Quality of life
Systems Medicine in U-BIOPRED

CT-scans

Lung function

Bronchial biopsies

Questionnaires

Breathomics

Sputum

GWAS

Transcriptomics

Proteomics

Lipidomics
The Handprint of Severe Asthma

- metabolomics
- proteomics
- clinical data
- transcriptomics/genomics

PRO*

* Patient-reported outcomes

systems biology
Open source knowledge management platform

tranSMART Data Warehouse

Mining

Curation/ETL

Source Data

Clinical Trials
- Analysis Results
- Clinical Data
- RBM
- mRNA
- SNP
- Metabolomics

Non-Clinical Gene Expression

Curated Content

Text Corpus
- Documents, Shared Folders, Conference Abstracts

Master Data

Szalma et al. J Translational Med 2010;8:68
Metabolomics - Breathomics

Exhaled markers → Sensor analysis → Pattern-recognition

Training and validation sets by eNose: asthma versus COPD

Accuracy: 85%

AUC: 0.93

The U-BIOPRED Consortium

- Biopharma Companies 9
- Multinational Industry 1
- Patients & Care Organisations 6
- SME’s 3
- Academia 20
- Regulators 1
- SME’s 3
- Academia 20
- Patients & Care Organisations 6
- Regulators 1
- Biopharma Companies 9
- Multinational Industry 1
1. Reaching international consensus on diagnostic criteria
2. Creating adult/pediatric cohorts and biobanks
3. Creating novel phenotype ‘handprints’ by combining molecular, histological, clinical and patient-reported data
4. Validating such ‘handprints’ in relation to exacerbations and disease progression
5. Refining the ‘handprints’ by using preclinical and human exacerbation models
6. Predicting efficacy of gold-standard and novel interventions
7. Refining the diagnostic criteria and phenotypes
8. Establishing a platform for exchange, education and dissemination
CNRS-EISBM EU Projects in Rhône-Alps

Structuring Effect on Regional and European Levels

- **U-BIOPRED** -24 M€- (2009-2014)
  - Unbiased Biomarkers for the Prediction of Respiratory Disease outcomes
  - 40 partners
  - Including 10 big pharma
  - IMI exemplar project

- **eTRIKS** -24 M€- (2012-2017)
  - Developing and Deploying a European Translation Information & Knowledge Management Service Infrastructure
  - 6 partners (academics+SMEs) +10 big pharma EFPIA
  - Deliver Knowledge Management Platform
  - Structuring effect for IMI, FP7 and Horizon 2020

- **MeDALL** -14 M€- (2010-2014)
  - Mechanisms of the Development of Allergy
  - 23 partners (academics + SMEs)

- **AirPROM** -16 M€- (2011-2016)
  - Airway Disease PRedicting Outcomes through Patient Specific Computational Modelling
  - 33 partners (academics + SMEs)

- **SysCLAD** -4 M€- (2012-2014)
  - Systems prediction of Chronic Lung Allograft Dysfunction
  - 8 partners (4 academics, 4 SMEs)
  - Based on existing lung transplantation cohort

- **Synergy-COPD** -5 M€- (2011-2016)
  - Modelling and simulation environment for systems medicine (Chronic obstructive pulmonary disease -COPD- as a use case)
  - 8 partners (academics + SMEs)

- **CASyM** -4 M€- (2012-2016)
  - Coordinated road map to implement Systems Medicine across Europe
  - 23 partners (academics, SME, industry, hospitals, government, patient org)

- **SysPatho** -3 M€- (2011-2014)
  - Inserm Systems Biology of Hepatitis C infection
  - 11 partners (9 academics, 2 SMEs)

- **Lyonbiopole-EISBM** Information and Knowledge Management Services (TRI Bioaster ICT platform)

- **Network of Systems Medicine Centres** (Horizon 2020)

- **Microbiome** TRI (Bioaster experimental platforms)

- **Strengthen involvement of clinicians and SMEs in Systems Medicine** (HCL, CHU Grenoble)

- **Bioenergetics Exercise**

- **CENS Nutrition**
Airway models

A, airway model using CT data to fit airways down to branch generations 6–9
B and C flow in zones with different alveolar, arterial and venous pressure

©2004 by The Physiological Society
MeDALL is a collaborative project supported by the European Commission under the Health Cooperation Work Programme of the 7th Framework programme.
SysCLAD: Systems prediction of Chronic Lung Allograft Dysfunction

• FP7-Health Systems Medicine: SME-driven research applying systems biology approaches to address medical and clinical needs

• Coordinator: Laurent Nicod, Centre Hospitalier Universitaire, Lausanne, Switzerland; CHU Nantes; CHU Grenoble; Four SMEs: Finovatis, Novadiscovery, Lyon; Biomax, GATC, Germany.

• Based on COLT cohort in lung transplantation (11 centres in France) with established eCRF, SOPs and biobank extended to Swiss (Lausanne, Zurich) and Belgium (Brussels) centres
Medical Need: Burden of Respiratory Diseases

- Shortage of grafts, Primary Graft Dysfunction
- Chronic Lung Allograft Dysfunction
  - BOS in 50% at 5 years
  - different patterns
  - 30% cause of death > 1 year
  - median survival 1.5 years, if early onset

-15%, 3 months
- 4% / year
Delivering European Translational Research and Information Management Services (eTRIKS)

• IMI Round 4 Project

• Objective:
  – Provision of a sustainable KM Platform and Service to support Private/Public Translational Research (TR) in IMI and beyond
  – Single access point to standardised curated TR study information

• Scope:
  – Cloud Hosting, KM Platform, Data & Service Standards, Analytics, Curation, and Training

• Members:
  – 10 Pharmaceutical Companies
  – 6 Academic Partners/Commercial Suppliers

• Budget: €23.98m for 5 years (Oct 2012-Sept 2017)
eTRIKS Architecture

Based entirely on open source software
Support project-level multi-tenancy
The CASyM consortium: 22 partners from 11 European countries

Full partners
GERMANY (6)
UNITED KINGDOM (3)
FRANCE (3)
SWEDEN (2)
LUXEMBOURG (2)
NETHERLANDS (1)
SLOVENIA (1)
IRELAND (1)
ICELAND (1)
ITALY (1)

Associated partners
UK - OBC
GERMANY - BAYER
GERMANY - BioM Biotech
ESTONIA - Estonian Genome Center,
IRELAND - Science Foundation Ireland
(under discussion)
Major Objectives of the Coordination Action CASyM

*Engagement of key stakeholders from all significant areas
*Developing a clear strategy and a practical road map for sustainable implementation of Systems Medicine across Europe
*Interaction with key national and European Systems Medicine initiatives
Coordinating Systems Medicine across Europe
European Systems Medicine road-map discussions

From Systems Biology to Systems Medicine Workshops
   June 2010 - Brussels
   January 2011 - Barcelona
   June 2012 - Brussels
Systems Medicine Conference - September 2012 - Dublin

EU-CASyM joint workshop
   November 2012 - Brussels

CASyM stakeholder meeting
   March 2013 - Lyon
Integrative Systems Biology & Medicine

Predictive, Preventive, Personalized, Participatory Medicine

Predictive and preventive vs reactive
Personalized and participatory vs same treatment for all

Multi-parameter blood diagnostic
Drugs targeting network nodes

Escalating cost and attrition rate in drug development
Classification/stratification of diseases and patients

Systems biology and personalized medicine – the future is now

Revolutionizing medicine in the 21st century through systems approaches

Consortium SYSTEMOSCOPE
« Rethink research, understand life, improve health »