Computational Toxicology

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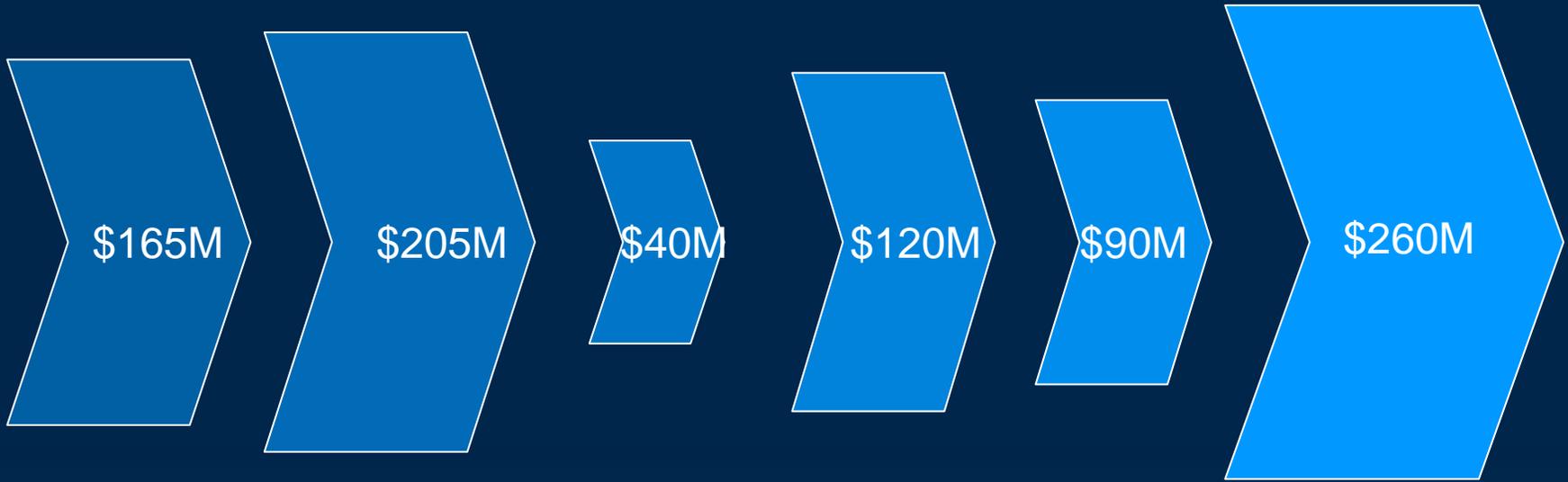
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Overview

> Background

> Aim

> Cells and proteins

> Network analysis

> Computational toxicity prediction

> Experimental validation

> Conclusions

Drug development process

| Target ID	Target validation	Screening	Optimisation	Pre-clinical	Clinical
$165M	$205M	$40M	$120M	$90M	$260M

Toxicology

(BCG, 2001)

Toxicology and drug development

➢ Animal tests – expensive

➢ In-silico testing – much less expensive

➢ Significantly reducing toxicology costs may reduce by 5-8% the total costs of drug development, and by 12-20% the pre-clinical and clinical phase costs of drug development

Aim of the project

➢ The project aims to develop new experimentally validated computational toxicology methods that can reduce significantly the costs of toxicological evaluation of drug compounds.

Cells – protein interaction systems
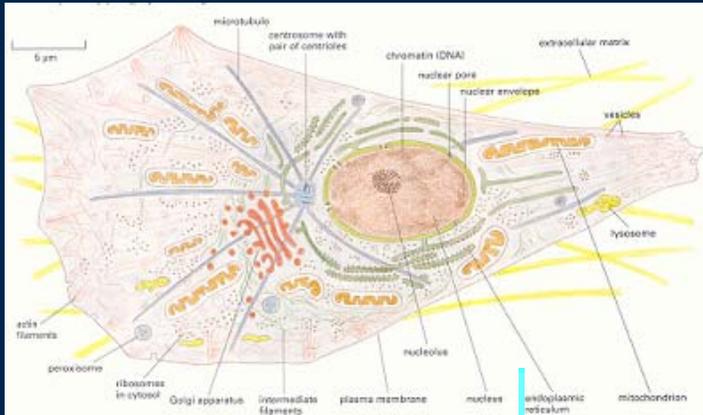
Proteomics data – Proteins

- Swiss-Prot, KEGG, EBI-Proteome

- Sequence, gene, function

Proteomics data - interactions

➢ DIP, STRING, SPiD

➢ Interactions between proteins (yeast-two-hybrid, tandem-affinity purification, prediction)

➢ Interaction systems – network of interactions

Data collection and management

➢ Building of a data interface that downloads and regularly updates protein and protein interaction data available from public web databases

➢ Local database in XML

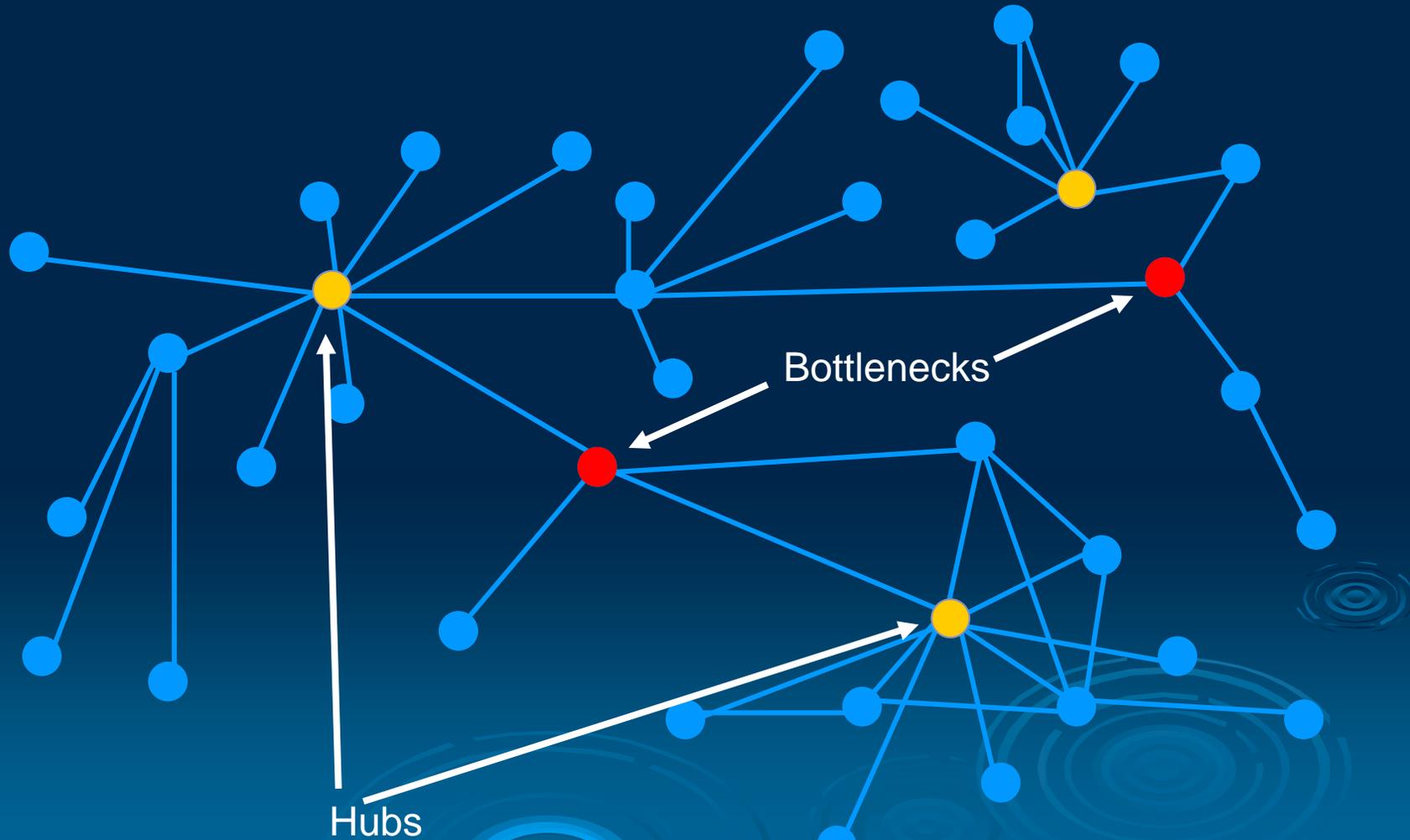➢ Link to web databases for additional information

Networks – structural integrity

Measures:

- average minimum path length
- average clustering coefficient

Networks – important components

Bottlenecks

Hubs

Structural and functional integrity

➤ Protein interaction networks are scale-free networks → high tolerance of random damage, high sensitivity to targeted damage

➤ Jeong et al., 2001: 70% of hubs in yeast protein interaction network are essential proteins (in resource rich medium)

➤ Structural integrity of interaction networks correlates with functional integrity of the represented proteome

Drug compounds and proteins

➢ Binding between drug compounds and proteins (e.g., penicillin and PBPs)

➢ List of host organism proteins that are affected by the drug compound

- computational analysis – search for binding domains
- experimental analysis – 2D gel electrophoresis signature

Analysing the role of proteins

➢ Network analysis of the protein interaction network of host organism

➢ Output: contribution of selected proteins to the structural integrity of the host protein interaction network

H. sapiens protein interaction network
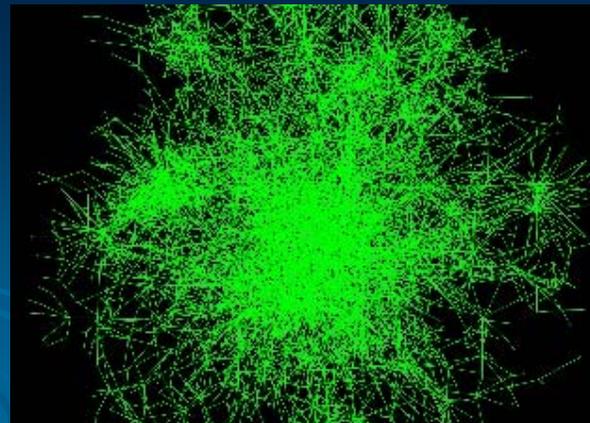
Importance of network components

➢ Connectivity number

➢ Neighbourhood clustering coefficient

➢ Bottleneck coefficient

➢ Elementary cycle number

# Contribution to network integrity

➢ Average shortest path

➢ Average clustering coefficient

➢ Effect on characteristic polynomial

➢ Effect on eigenvalues

Toxicity prediction

➤ Contribution of affected proteins to the structural integrity of the host protein interaction network → measure of potential structural damage

➤ Structural damage → prediction of functional damage = toxicity prediction

Bacillus subtilis

➢ Experimental validation using *Bacillus subtilis*

Protein interaction network of *B. subtilis*
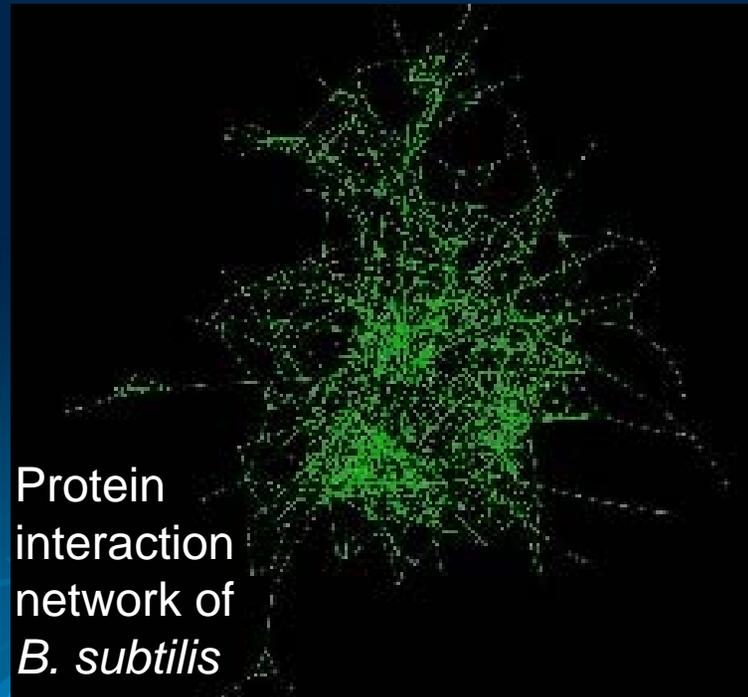
Toxicity prediction for drug compounds

➢ Set of drug compounds: antivirals (e.g., ribavirin), antibiotics (e.g., chloramphenicol), other drugs (e.g., propranolol)

➢ Determination of affected *B. subtilis* proteins (computational analysis, 2D gel electrophoresis signature)

➢ Evaluation of the structural integrity contribution of affected proteins in the context of the protein interaction network and toxicity prediction for the drug compound

Experimental validation

> *B. subtilis* cultures

> Measure and compare growth rate / yield in presence and absence of drug compound

> Does the toxicity prediction correlate with the measured effect on growth rate / yield ?

Work plan

Work package \ Month	1	2	3	4	5	6	7	8	9	10	11	12
1. Database construction	██	██										
2. Computational toxicology toolkit development		██	██	██	██	██	██	██				
3. Analysis of *B.subtilis*							██	██	██	██		
4. Refining the method									██	██	██	██

Expected outputs

➢ A new experimentally validated computational toxicology methodology that can help in reducing significantly the costs of drug development

➢ Publications (1-2) in major discovery journals

➢ Presentation of the results at major conferences

Collaborations

➤ Prof Colin Harwood – *B. subtilis* experimental work and biological analysis

➤ Other collaborators: Dr Anil Wipat, Dr Alan Ward, Prof Malcolm P Young

Summary

- Computational toxicology may help to significantly reduce drug development costs
- Structural integrity of protein interaction systems correlates with their functional integrity
- Contribution to network structural integrity of host proteins affected by a drug compound indicates the toxicity of the drug compound
- Network analysis to determine the role in structural integrity, prediction of drug toxicity
- Experimental validation using *B. subtilis*