

Computational Toxicology


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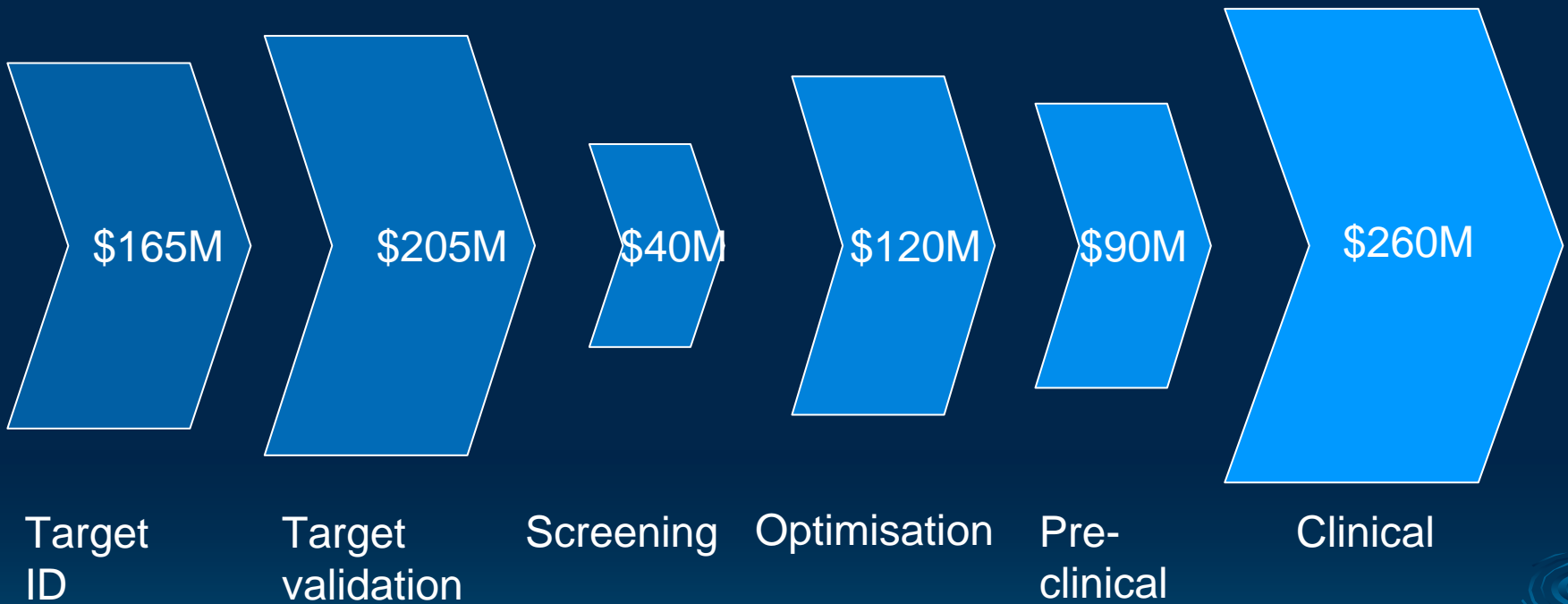
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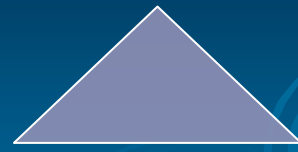
Overview

- Background
 - Aim
 - Cells and proteins
 - Network analysis
 - Computational toxicity prediction
 - Experimental validation
 - Conclusions
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Drug development process



(BCG, 2001)



Toxicology

Toxicology and drug development

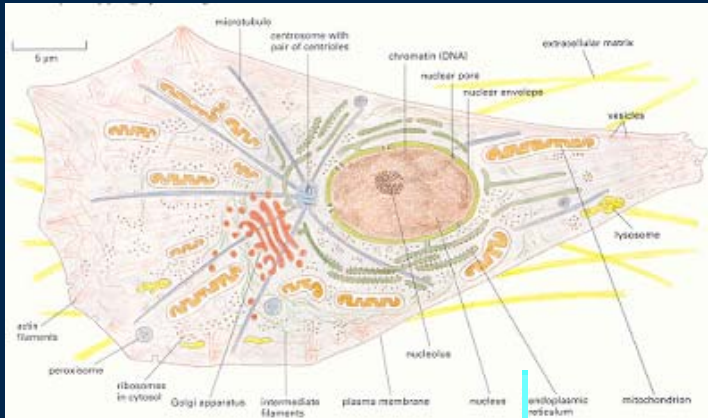
- Animal tests – expensive
- In-silico testing – much less expensive
- Significantly reducing toxicology costs may reduce by 5-8% the total costs of drug development, and by 12-20% the pre-clinical and clinical phase costs of drug development

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
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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
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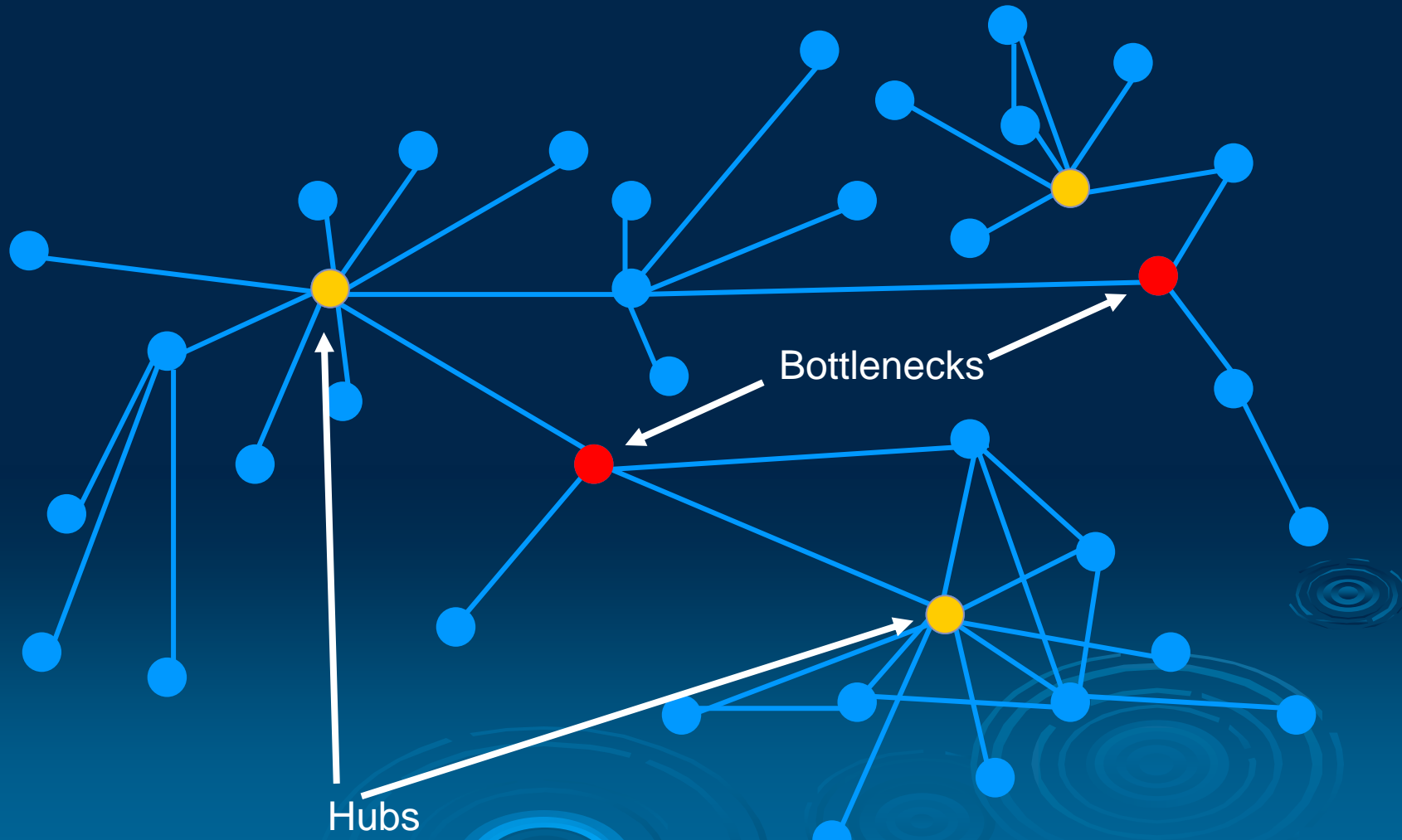
Networks – structural integrity



Measures:

- average minimum path length
- average clustering coefficient

Networks – important components



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

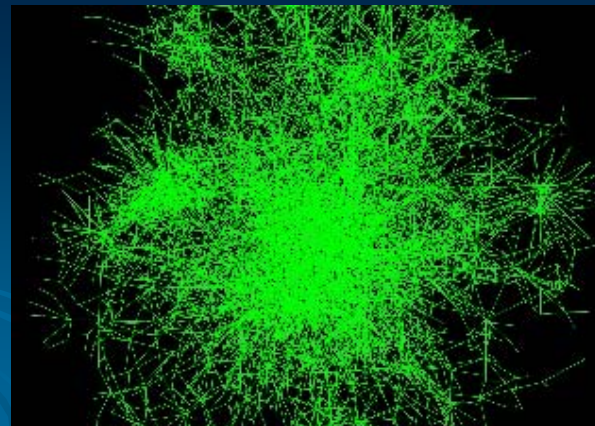
Drug compounds and proteins

- 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
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Contribution to network integrity

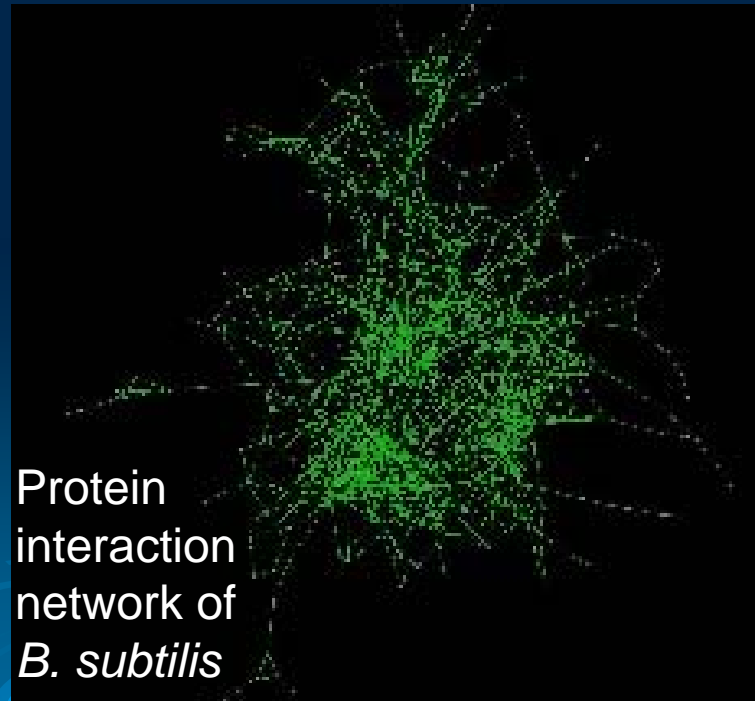
- Average shortest path
 - Average clustering coefficient
 - Effect on characteristic polynomial
 - Effect on eigenvalues
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Toxicity prediction

- 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*



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

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