INFLUENZA VIRUS-HOST PROTEIN-PROTEIN INTERACTION NETWORKS: ENGINEERING INSIGHTS INTO HOST-VIRUS INTERACTIONS

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EFFICIENT ANTIVIRAL DRUG TARGET DEVELOPMENT IS NEEDED TO ADDRESS GLOBAL INFLUENZA VIRUS INFECTION

In the US from 2011-2016
9.2 million - 35.6 million cases
140,000 - 710,000 hospitalizations
12,000 - 56,000 deaths

Limited drug options
• Oseltamivir
• Zanamivir
• Peramivir**

**Not recommended for children and people with breathing problems

Question: Can virus-host protein interaction data be used to predict drug target candidates in a novel ways?

Rofles, M. A. Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States | Seasonal Influenza (Flu) | CDC. (2016).
TWO APPROACHES TO DRUG TARGET DISCOVERY

1. Exploit siRNA virus replication screening data to isolate subnetworks enriched for drug targets

2. Apply network controllability to characterize virus control of host cells and ID drug targets

Using: Virus-host interaction data
INFLUENZA PROTEINS INTERACT WITH PROTEINS IN SIGNIFICANT NETWORK POSITIONS

Topology distinctions are too minor to provide legitimate guidance for drug discovery.
A NEW METHOD FOR TARGET HOST PROTEIN IDENTIFICATION USING VIRUS-SPECIFIC SUBNETWORKS

Analyze subnetwork proteins for new antiviral drug candidates
Betweenness is altered when adding virus-host interactions.

Betweenness may help prioritize candidates within the subnetwork.
SUBNETWORK AND NETWORK POSITION ARE POWERFUL PREDICTORS OF ANTIVIRAL DRUG TARGET CANDIDACY
ROLE OF SUBNETWORK PROTEINS DISTINCT FROM VIRUS-INTERACTING PROTEINS

**Virus-interaction:**
- Virus replication
- RNA transcription
- Protein translation

**Subnetwork:**
- Immune response
- NFkB
1. Integrating virus-host interactions, screening data and network topology can improve antiviral discovery

2. Subnetwork approaches isolates key pathways that viruses must regulate to promote replication
Previous work focuses on the topology of a “static” network.

**Question:** How can the network be manipulated by a virus to influence specific biological pathways?
To control a system, individual states must be driven to desired values.

Viral infection can be modeled as a controllability problem.
GOAL: IDENTIFY KEY PROTEINS IN NETWORK MANIPULATION DURING IAV INFECTION
BETWEENNESS DEMONSTRATES THE WIDE EFFECTS OF VIRAL PROTEIN INTERACTIONS

IAV interacting proteins (blue) significantly shift degree

752 IAV interacting proteins

2,705 proteins increase in betweenness

IAV interacting proteins have significantly higher betweenness compared to all proteins in respective networks (p-value: $2.1 \times 10^{-15}$ and $2.2 \times 10^{-16}$, respectively)
MAGNITUDE OF CONTROL IS UNCHANGED AFTER ADDITION OF VIRAL INTERACTIONS

Driver proteins:
Minimum protein set that must be manipulated to control a system (non-unique)

After infection:
Same proteins with 11 exceptions (IAV proteins)

8.9% of driver proteins are also IAV interacting
Significant betweenness compared to non-IAV interacting driver proteins (p-value: 2.2×10^{-16})
CONTROLLABILITY TYPES OFFER DIFFERENT INFORMATION ABOUT THE NETWORK

LIU ANALYSIS IDENTIFIES NO CHANGE IN CONTROL BEHAVIOR DURING INFECTION

The absence of single proteins does not alter the control structure of the infected system.

Fails to detect known changes in immune response and transcriptional processes.

Observe changes to control structure in absence of nodes.
JIA ANALYSIS IDENTIFIES KEY PROTEIN SET ASSOCIATED WITH HOST IMMUNE RESPONSE

24 host proteins shift Jia classification

All possible control configurations → some possible control configurations

All identified proteins are both driver and IAV interacting proteins

IAV interacting proteins are not enriched for driver proteins (p-value: 0.14)
JIA analysis identifies key protein set associated with host immune response.

Liu method identifies proteins whose network significance is not altered by infection.

Jia method identifies proteins which have no network significance in the healthy cell (betweenness of 0) and high network significance during infection.
Protein set functions (IPA):

*Jia* (24 driver/IAV interacting):
- Protein synthesis, centered around NF-κB
- Cell infection (*EPHA2, FBL, PFKM, PSMA5, SSR1, and TFRC*, p-value: $9.58 \times 10^{-4}$)

*Liu* (11 changing drivers) *and Jia* both identify:
- mRNA processing (*CELF1, HNRNPA0, SF384, and SRPK2*, p-value: $3.33 \times 10^{-6}$)

Interferon regulated genes:
- *Liu*: 11/11
- *Jia*: 20/24

6 *Jia* proteins identified in >10 studies
PROTEINS IDENTIFIED BY CONTROLLABILITY ARE NOT ENRICHED FOR VALIDATED IAV HOST FACTORS

Validation data from 6 siRNA screens for host factors involved in influenza replication

**Liu:** 2/11 validated (fisher test p: 0.685)
SF3B4  SRPK2

**Jia:** 5/24 validated (fisher test p: 0.252)
OSMR  PPA1  PSMA5  POLE4  GDI2

Genes of interest may be outside of partial genome screens

What should be screened next?
Integrating IAV interactions into existing PPI networks has cascading effects on network topology

- Wide reaching effects

IAV interacting driver proteins are in significant positions for network flow
IAV-HOST PROTEIN INTERACTIONS OFFER THE GREATEST ADVANTAGE FOR CELL MANIPULATION

**IAV interacting proteins:**

- Make the network more difficult to control in their absence
  - **Gateway to system control**
- Are often **integrated** into control configurations (opposed to being driver proteins)
- Responsible for the **ease and propagation of control through the system**
DRIVER PROTEINS RAISE INTERESTING QUESTIONS FOR THE FUTURE OF DRUG DESIGN

**Driver proteins:**

Make the network easier to control in their absence
Weak point in host defense

Play varying roles in different control configurations
Versatile role

One possible drug target development strategy is to promote the protection of driver proteins
HOST-VIRUS INTERACTIONS CAN BE APPROACHED WITH MULTIDISCIPLINARY TOOLS TO EFFICIENTLY IDENTIFY DRUG TARGET CANDIDATES

**Experimental biology:** Identifies and publishes large amounts of PPI data, available for use instantly (*Efficiency!*)

**Network Science:** Supplies tools to organize and analyze PPI data using topology measures, enables “whole cell” view of infection

**Engineering:** Provides methods to analyze key factors within the cell system which control infection behavior
THANK YOU

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NETWORK CONTROLLABILITY DIRECTLY EVOLVES FROM CLASSIC CONTROLLABILITY

a) Network representation

b) State space representation

\[
A = \begin{bmatrix}
0 & 0 & 0 \\
0 & 0 & 0 \\
0 & 0 & 0
\end{bmatrix},
B = \begin{bmatrix}
b_1 & 0 \\
0 & b_2 \\
0 & 0
\end{bmatrix}
\]

where:

- \( A \) = Interaction weight matrix
- \( x \) = Protein concentration state matrix
- \( B \) = Input process weight matrix
- \( u \) = Protein translation process input matrix

\[
\dot{x} = Ax + Bu
\]

\[
\dot{x} = \begin{bmatrix}
0 & 0 & 0 \\
a_{21} & 0 & 0 \\
a_{31} & 0 & 0
\end{bmatrix}\begin{bmatrix}
x_1 \\
x_2 \\
x_3
\end{bmatrix} + \begin{bmatrix}
b_1 & 0 \\
0 & b_2 \\
0 & 0
\end{bmatrix}\begin{bmatrix}
u_1 \\
u_2
\end{bmatrix}
\]

c) Controllability matrix

\[
C = \begin{bmatrix}
B & AB & A^2B
\end{bmatrix}
\]

\[
C = \begin{bmatrix}
b_1 & 0 & 0 & 0 & 0 & 0 \\
0 & b_2 & a_{21}b_1 & 0 & 0 & 0 \\
0 & 0 & a_{31}b_1 & 0 & 0 & 0
\end{bmatrix}
\]

Rank \((C) = 3\)

Full rank

\(\therefore\) System is fully controlled