Introduction to Systems Biology
Lecture 11 Part A-1

Iyengar

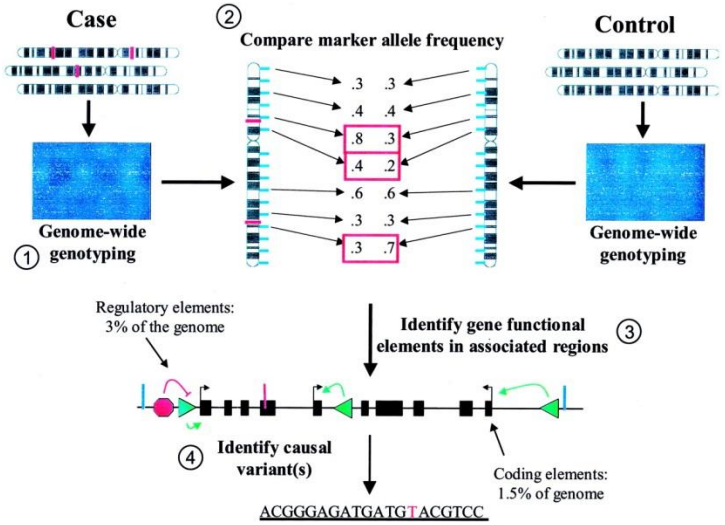
Strengths and Limitations of Different Types of Models

Statistical Models Usefulness of bookends in defining biological functions for systems level studies

Gene(s) → Disease (phenotype)

Clinical diagnosis is most often a well-defined physiological function

Other molecular co-relates of the physiological function can provide context to understanding the role of gene(s) of interest



Schematic of Genome – Wide Association Study
Arking D, E et al Circulation Research 2004 94: 712

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Statistical Models – Ability to capture probabilistic relationships

For most complex disease (phenotypes) the association of gene(s) is often probabilistic

Statistical models enable the representation of such probabilistic relationships

An example is a proposed causal inference test by Eric Schadt and co-workers

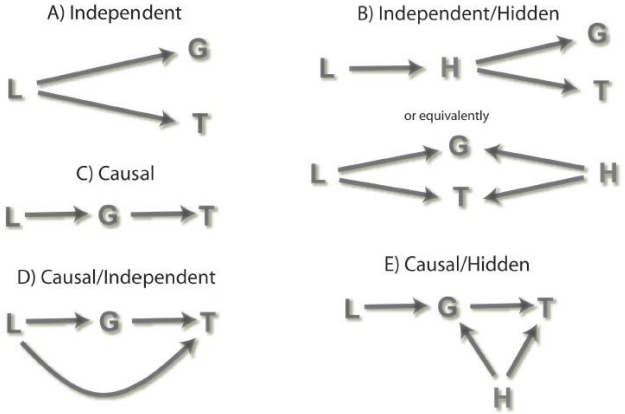

Figure 4. Four causal inference strategies, CC, CIT, BNC, and AIC were applied to simulated data under five distinct causal models, A-E, shown above. Here a genotype marker at a specific locus is denoted by L, a gene corresponding to measured transcript abundance is denoted by G, and a measured clinical trait is denoted by T. H denotes an unmeasured molecular trait.

Millstein J et al BMC Genet(2009) 10:23

Statistical Models obscure mechanistic details

Statistical models typically do not consider mechanisms (e.g. CNV or DNA methylation) that control the expression of the gene (protein) of interest

Statistical models do not consider details of a pathway of action in measuring a relationship between gene (protein) of interest and phenotype

Not considering mechanistic details can sometimes lead to missing clues for additional proteins/genes involved in the phenotype (disease)

Not considering mechanistic details can sometimes lead co-relations to fail due to effects of modifiers.

Statistical Models do not provide dynamic or spatial information

Most statistical tests assume a steady state relationship between gene(s) (protein(s)) and the phenotype being measured.

For complex diseases phenotypes change with time and treatment (e.g. developing resistance to a drug). It is often necessary to capture these details if statistical model based tests are to be developed.

For many biological functions at a cellular level spatial specification is essential for understanding function - this is not represented in statistical models

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Network models are essential for understanding the topology of the system

Need to know the lay of the land

Networks are similar to subway maps

Can tell you how get from here (genes) to there (proteins, functions, phenotypes)

what routes can (are) be taken

Where points of connections are

Understanding topology (organization) is an essential part of understanding the system !

From Wikipedia, the free encyclopedia

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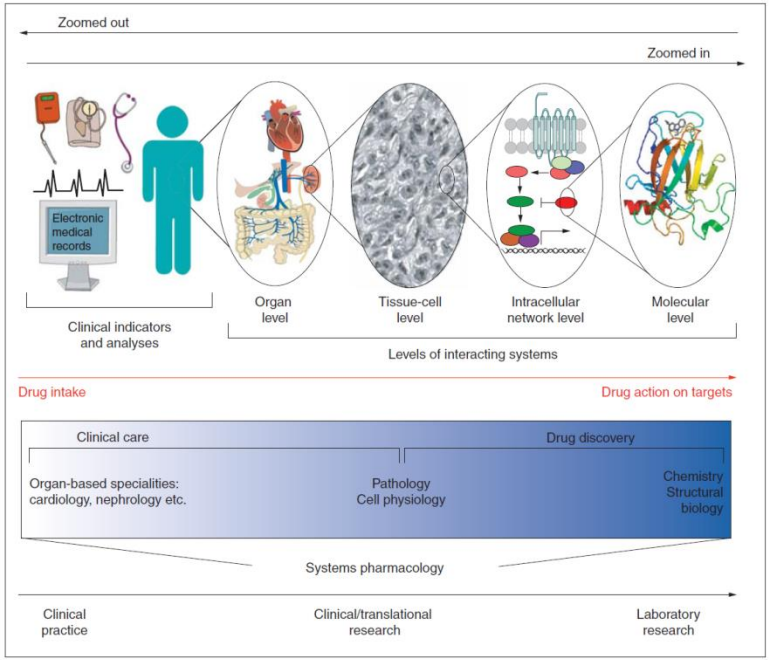
Network models are flexible and can be used for multiscale descriptions of a system

The user definition of edges allows networks to built with a single scale or between scales of interaction

Same node can be part of networks in one scale and between scales

Such network models allow us to understand how effects of interaction at one level can affect function at another level



Wist, Berger and Iyengar (2009) Genome Medicine 1:11

Network model provide good description of the regulatory or information processing capability of the system

Directed sign-specified graphs are required to identify the presence of feedback and feed forward loops in networks

Since such loops have the capability of process information, identifying the presence of such loops allows inferences regarding the information processing ability of the system

Information processing leads alteration of input/output relationships

Change in I/O relationships lead to state change in many cell types

To understand state change such disease origins one needs directed sign-specified network models of the cell/tissue of interest.