Computational Systems Biology of Cancer Metastasis

Cancer Systems Biology group
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Cancer metastasis: an unsolved clinical challenge

- Metastasis - the spread of cancer cells from one organ to another - causes more than 90% of all cancer-related deaths.

- Cancer cells largely spread by traveling in blood vessels in our body.

- Metastasis is an extremely challenging process for cells, with very high (> 98%) rates of attrition.
What traits cells need to successfully metastasize?

- Dynamic/Adaptive changes in:
  - Cell-cell adhesion
  - Ability to migrate and invade
  - Evading attacks by immune system
  - Settling down in a new organ and colonizing it
  - Resist multiple therapies/drugs given to patients

Thus, to restrict metastasis, we first need a **dynamic and systems-level understanding** of the process to identify how cells alter these multiple traits together.
A systems-level understanding means…

1. Realizing that integrating different parts can lead to novel behaviors/functions, i.e. whole is greater than sum of its parts

2. Being able to predict the behavior of the system in varied conditions

We can mathematically model these biological networks to achieve a systems-level understanding, similar to that attained for engineered systems as shown above.
EMT/MET: An engine of metastasis

More than 80% cancers begin in epithelial organs. Cancer cells reversibly transition to a mesenchymal state – a phenomenon known as Epithelial-Mesenchymal Transition (EMT) – that enables them to migrate, invade, and eventually enter blood circulation. Reverse of EMT – MET – helps them to colonize other organs after exiting circulation.

Adhere to neighbors
Do NOT migrate or invade
**Epithelial (E)**

Do NOT adhere to neighbors
Migrate and invade
**Mesenchymal (M)**

**Mesenchymal-to-Epithelial Transition (MET)**

**Epithelial-to-Mesenchymal Transition (EMT)**

Scheel & Weinberg, Semin Cancer Bio 2012
A systems biology approach to understanding EMT

Mathematical model’s prediction

1. EMT is not a binary process – cells can attain an E, M, or a hybrid E/M state stably
2. Cells with same genetic background (isogenic) can contain multiple co-existing subpopulations (E, M, E/M)

Experimental validation

- H1975 (cultured over 2 months); CDH1 (E-marker), VIM (M-marker)
- Stable existence of a hybrid E/M state

Co-existence of phenotypes in a cell line

Jolly et al. Oncotarget 2016
George*, Jolly* et al. Cancer Res 2017
A generalized systems biology workflow

Steps involved in ITeRaTe workflow:

1. Identify core players regulating a specific biological property based on published experimental data (gene expression profiles, qPCR/Western Blot data, RNA-seq/ChIP-seq data, knockdown/overexpression experiments etc.)

2. Construct regulatory network formed among those players by putting together their interconnections

3. Simulate the dynamics of regulatory network; compare with experiments, propose new experiments to do

Jolly et al. Pharmacol Therap 2018, in press
Tools and techniques used

- Mathematical modeling of biological regulatory networks
- Simulating a set of ordinary (and/or partial) differential equations
- Analyzing experimental transcriptomics/proteomics, and clinical data

Required background

- Basic understanding of ordinary differential equations and nonlinear dynamics (or will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in both cancer biology and systems biology)

**Note:** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology
Further reading

