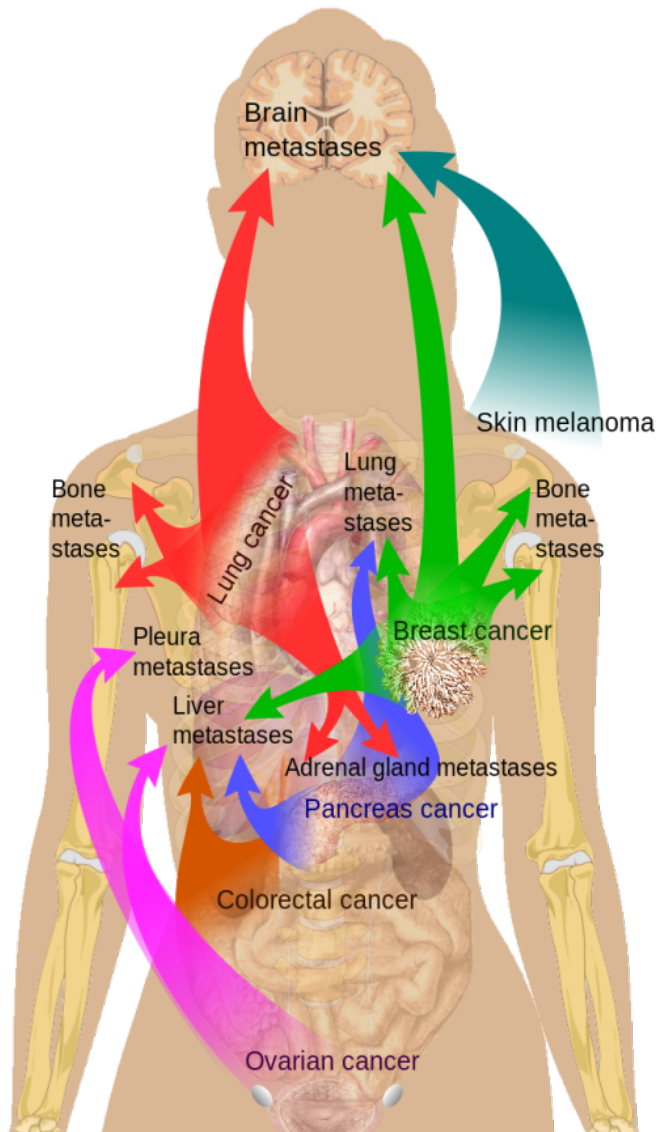# Computational Systems Biology of Cancer Metastasis

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

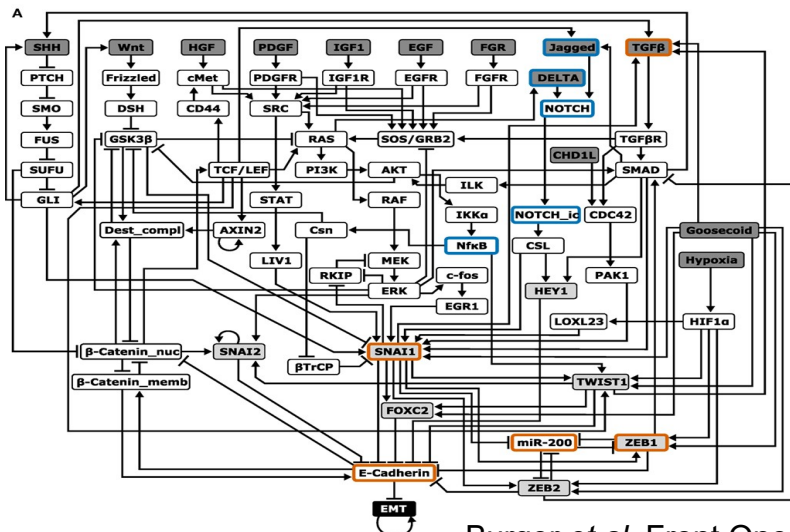# What traits cells need to successfully metastasize?

- 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 <u>a dynamic and systems-level understanding</u> 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

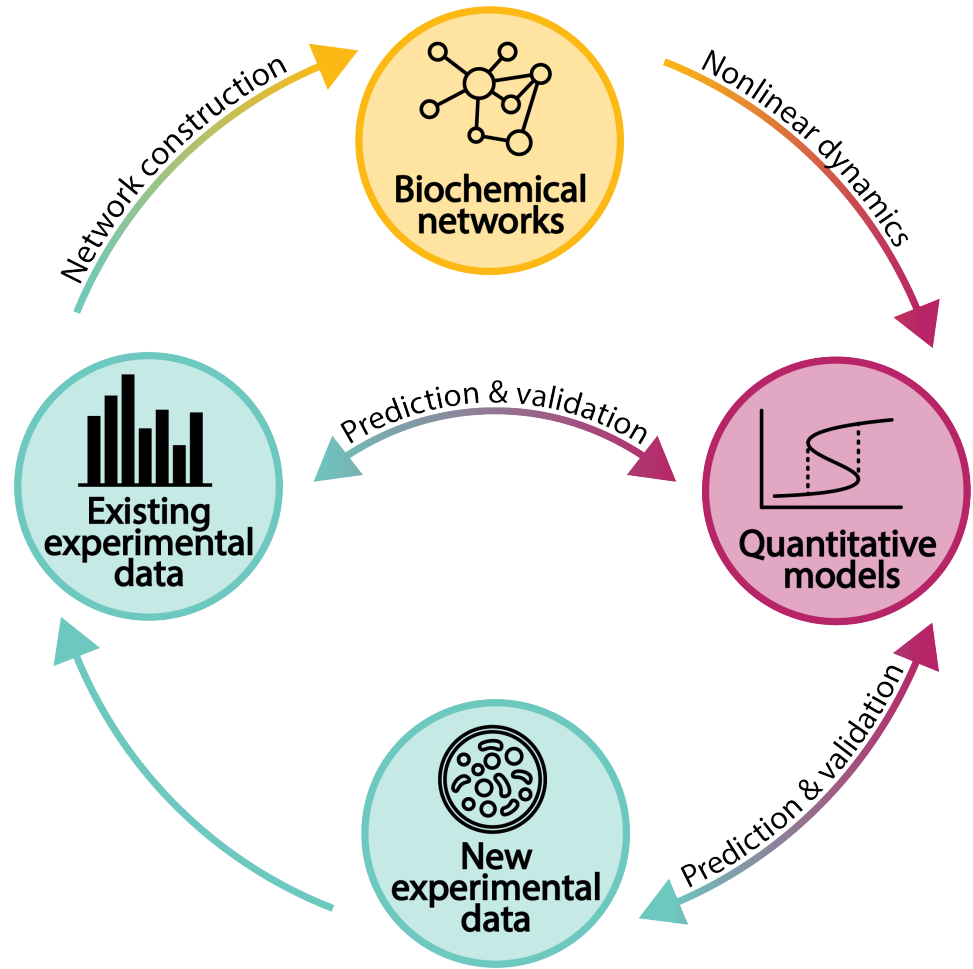2. Being able to predict the behavior of the system in varied conditions

We can mathematically model these biological networks to achieve a systems-level understanding, similar to that attained for engineered systems as shown above

Burger *et al.* Front Oncol 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

Input, Test, Refine, and Test (ITeRaTe)

Network construction

Biochemical networks

Nonlinear dynamics

Prediction & validation

Existing experimental data

Quantitative models

New experimental data

Prediction & validation

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 the self-driven will to acquire them)
- Keen interest in pursuing interdisciplinary research (i.e. reading literature in both cancer biology and systems biology)
- **<u>Note:</u>** Students from physics/chemistry/mathematics/engineering background are welcome too, provided they show interest in acquiring the relevant understanding of biology

Further reading

- Kolch, W.; Halasz, M.; Granovskaya, M.; Kholodenko, B. N. The dynamic control of signal transduction networks in cancer cells. Nat. Rev. Cancer 2015, 15 (9), 515–27. doi: 10.1038/nrc3983

- Magi, S.; Iwamoto, K.; Okada-Hatakeyama, M. Current status of mathematical modeling of cancer – From the viewpoint of cancer hallmarks. Curr. Opin. Syst. Biol. 2017, 2, 38-47. doi: 10.1016/j.coisb.2017.02.008